EGGERT Ó. JÓHANNSSON

THE PELGER ANOMALY

GENETIC, CYTOLOGIC AND EPIDEMIOLOGIC ASPECTS OF SOME DATA FROM SWEDEN

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THE PELGER ANOMALY

Genetic, cytologic and epidemiologic aspects of some data from Sweden

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BY

Eggert Ó. Jóhannsson

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To my wife

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INTRODUCTION

The Pelger-Huët nuclear anomaly is a dominantly inherited leukocyte variation. Stained blood smears from individuals, who are heterozygous for the gene determining the anomaly, show the following major characteristics:

a. An almost complete absence of neutrophils with more than two lobes in their nuclei.
b. The vast majority of the neutrophils have either unsegmented, dumb-bell shaped, or bilobed spectacle-like nuclei and a typical coarse chromatin structure.

In the homozygous state only unsegmented nuclei are found in the neutrophils.

No association has been established between the Pelger anomaly and any disease.[1]

The anomaly has been found in all parts of the world and in all races. Frequencies up to 1 per 1,000 have been found in some European populations. There are no extensive data available on its world-wide incidence or geographical differences in frequency.

The term "partial form of Pelger anomaly" ("Teilträger" or "partial carrier") has been used to denote a condition whose relationship to the true Pelger anomaly is not clear. In the "partial form" only a certain proportion of the neutrophils shows the characteristics of the heterozygous state of the Pelger anomaly.

[1] Strictly speaking, one must consider the Pelger anomaly as a "disease." In the present context Pelger "anomaly" is used in the sense of a specific structural deviation from the normal without any other known associated functional abnormalities.

The expressions "acquired Pelger anomaly", "Phenocopy of the Pelger anomaly" and 'Pseudo Pelger-anomaly" describe the occurrence of Pelger-like changes in certain diseases.

Some historical data

In 1928, at a meeting in the "Nederlandsche Ziektekundige Vereening," the Dutch hematologist Pelger (1928, 1931) described "a rarely occurring type of leukocyte," which he considered to be pathological. His findings are only briefly mentioned in the proceedings of the society, but are further referred to by Huët. Citing Huët (1932), the leukocytes found by Pelger were characterized by:

"1. eine sehr starke Linksverschiebung; es wurden mehr stabkernige als segmentkernige Leukocyten gefunden;
2. die Form der Stabkerne war, mit wenigen Ausnahmen, stets dieselbe: schöne, regelmässige Konturen, meistens mit einer einseitigen leichten Einbiegung in der Mitte.
3. Auch die Form der Segmentkerne zeigte ein eigentümliches Verhalten: sie bestanden fast ausnahmslos aus nur zwei Fragmenten, die durch ein dünnes Fädchen verbunden sind; es sind eben Stäbe, in denen die Einbiegung stärker ausgesprochen ist. Man findet dieses Verhalten sowohl bei den neutrophilen wie bei den eosino- und basophilen Leukocyten."

Pelger (1928) also noticed that the structure of the nuclear chromatin was "mosaic-like" and the unsegmented nuclei short and stubby. His first description thus included all the main morphologic characteristics of the blood picture of individuals heterozygous for the Pelger anomaly.

In 1931 Huët demonstrated that the leukocyte changes were inherited. Studies of other Dutch families (Huët 1932, Burger

1932, Jordans 1932) indicated that the anomaly behaved like a simple mendelian dominant. The anomaly was soon found also outside the Netherlands (Schilling 1933, Undritz 1933, 1934).

In 1937 Undritz described a leukocytic variation called "the partial form of Pelger anomaly" or the "Pelger-Teilträger" (Undritz 1937 a).

Leukocyte variations analogous to the Pelger anomaly and "the partial form of Pelger anomaly" found in man have been described in rabbits by Undritz (1943).

In 1942 Nachtsheim demonstrated that the Pelger anomaly is dominantly inherited in rabbits. He also described the blood picture of the homozygous Pelger anomaly in rabbits, which differs from that of the heterozygotes. In the former, neutrophils with segmented nuclei are completely absent. The homozygous form of the Pelger anomaly in man was first found in 1951 by Haverkamp Begemann & van Lookeren Campagne in the Netherlands.

The first cases of Pelger anomaly in Sweden were reported by Jonsson, Boström & Bringel in 1947. Since then the anomaly has, as far as I know, not been reported in Sweden. However, it has been described in the U. S. A. in people of Swedish extraction (Rosse & Gurney 1959).

Genetic aspects

Huët suspected that the leukocyte changes were familial, when he observed an unaccountable persistence of a "shift to the left" in the blood from a girl, who was a niece of one of the patients described by Pelger. The leukocytes strikingly resembled those described by Pelger, a fact that was confirmed by Pelger himself (Huët 1931 b, 1932). On examining other mem-

bers of this family Huët found that the leukocyte variation was an inherited anomaly.

As the reports on the Pelger anomaly accumulated in the literature, it was confirmed that the anomaly is dominantly inherited (Nachtsheim 1942).

No evidence has been found for linkage between the gene determining the Pelger anomaly and genes determining sex (Morton, Moloney & Fujii 1954, Davidson, Lawler & Ackerley 1954), ABO blood groups (Zündel 1936, Hardorn & Blum 1938, Morton, Moloney & Fujii 1954, Davidson, Lawler & Ackerley 1954), Rh blood groups or phenylthiocarbamid taste sensitivity (Morton, Moloney & Fujii 1954).

The Pelger anomaly has been found in persons of all ages (Nachtsheim 1950 a, Davidson, Lawler & Ackerley 1954).

Davidson, Lawler & Ackerley (1954) described an English family in which thirty-four of the members had the heterozygous Pelger anomaly. In the Pelger sibships the number of normal females was lower than the theoretically expected number. This applied both to sibships where the father or the mother had the Pelger anomaly.

The results from the family studies indicate that the Pelger anomaly is determined by a single gene. A possibility of multiple alleles was suggested, when some familial variation in the degree of nuclear lobulation in the neutrophils of individuals with the anomaly were found (Harm 1955 a, Nachtsheim 1950 b). This has, however, not been confirmed (Terhorst 1957).

Until 1951 the homozygous of the Pelger anomaly had only been found in rabbits. Then Haverkamp Begemann & van Lookeren Campagne (1951, 1952) claimed to have discovered a homozygous form of the anomaly in a Dutch girl. Her parents were consanguineous, and both of them were heterozygous for the Pelger gene. The neutrophils found in her blood were similar to those found in homozygous rabbits.

The homozygous form of the Pelger anomaly has since been reported in three otherwise normal adults by Bernard, Undritz, Bru, Mathé & Toulouse (1956) in Algeria, Ciplea & Ciorapciu (1958) in Rumania and Stobbe (1959 b) in Switzerland. However, only Stobbe could examine the relatives. The parents of the proband were dead, but one of his children was heterozygous for the Pelger anomaly (Stobbe 1959 b).

In the case described by Ciplea & Ciorapciu (1958) an abnormal cytoplasmic granulation was found in the neutrophils. The nuclear characteristics were also less marked than those described in the leukocytes of other individuals claimed to have homozygous Pelger anomaly. Stobbe (1959 b) has therefore pointed out that, in this individual, the evidence for homozygous Pelger anomaly is incomplete.

The Pelger anomaly has been reported in persons whose parents were normal (Zündel 1936, Stahel 1936, Jonsson, Boström & Bringel 1947, 1948, Jorde 1953, Scoler & Matter 1958, Skendzel & Hoffman 1962). It was considered unlikey that these persons were illegitimate. Two of them each had a child with the anomaly (Zündel 1936, Jorde 1953), but all the other relatives were normal.

Considering these "solitary" cases as new mutations of the anomaly, Nachtsheim (1954) estimated its frequency of mutation to be 2.7×10^{-5} per gene per generation. He calculated that the individuals heterozygous for the Pelger anomaly had about 95 per cent of the fitness of normal individuals.

In the first reported case of "the partial form of the Pelger anomaly" typical Pelger characteristics were noticed in 20 per cent of the neutrophils. The proportion of neutrophils with Pelger characteristics remained almost constant during nineteen years of observation (Petzel & Undritz 1957). Neither "the partial form" nor true Pelger anomaly was found in the relatives (Undritz 1937 a).

Subsequently "the partial form" of the anomaly has been described in three families with five affected individuals (Undritz 1954, Petzel & Undritz 1957, Undritz 1959). The findings in only one family with three individuals who had "the partial form" were suggestive of dominant inheritance (Petzel & Undritz 1957).

"The partial form" of the anomaly has been reported to occur in certain families, in addition to the true heterozygous form of the Pelger anomaly (Schuster 1949, Tischendorf 1939, Thiele 1952, Oehme 1953, Gutensohn 1954, Steffen & Heeger 1952). Harm (1955 b) reexamined some of these families and showed that the individuals previously found to have "the partial form" either had true Pelger anomaly or "acquired Pelger anomaly."

These findings of Harm tend to exclude the suggestion (Schilling 1952, Plettenberg 1945), that "the partial form" of the Pelger anomaly is merely a manifestation of variable expressivity of the true Pelger anomaly.

"The partial form" is probably an independent trait (Harm 1955 a, 1955 b, Nachtsheim 1942), of which the genetic mechanism is still unclear (Undritz 1960).

Nachtsheim (1942, 1943, 1950 a) studied the mode of inheritance of the Pelger anomaly in rabbits, and showed that it behaved as an autosomal dominant trait with complete penetrance. The blood picture of rabbits with the homozygous Pelger anomaly (called by Nachtsheim "Über-Pelger" or "Super-Pelger") differed from that of rabbits with the heterozygous Pelger anomaly (called by Nachtsheim "Vollträger") in that only unsegmented and mainly round nuclei with a very coarse chromatin structure were found in the neutrophils.

Nachtsheim (1942, 1950 a) and Undritz (1943) obtained an equal number of affected and normal offspring by mating normal rabbits and rabbits with the heterozygous Pelger

anomaly. Matings between rabbits with the heterozygous Pelger anomaly were expected to give affected and normal offspring in a ratio of 3:1. Instead, a ratio close to 2:1 and about 18 per cent of the expected number of homozygotes was obtained. Nachtsheim (1950 a) therfore concluded "..... that in a double dose the Pelger gene has a lethal effect and that the homozygotes perish as foetuses." However, some of the rabbits with the homozygous Pelger anomaly were born alive, but with few exceptions they died soon after birth. All of the rabbits homozygous for the Pelger anomaly were affected with severe skeletal malformations (Nachtsheim 1950 a).

Further studies of "the partial form" of the Pelger anomaly in rabbits yielded no clear evidence of heredity or relation to true Pelger anomaly (Nachtsheim 1942, Harm 1955 b).

Leukocyte nuclear morphology

The leukocyte characteristics in the heterozygous form of the Pelger anomaly show only a slight variability in the vast majority of reported cases (Undritz & Sepibus 1957).

In general, the neutrophils have distinctly outlined, unsegmented or bilobed nuclei, while tri-lobed ones occur sporadically. The nuclear lobes are connected by a thin strand of chromatin. They are either round, giving dumb-bell shaped or "spectacle-like" nuclei if symmetrical, or slightly elongated (fig. 3).

The unsegmented nuclei are short and stubby with an indentation of varying depth in their midportion. Round nuclei are infrequently seen in healthy heterozygotes (Undritz & Sepibus 1957).

Small nuclear protrusions ("small clubs") can be seen, and in females with the anomaly the sex specific "drumsticks" occur in a lower frequency than in normal females (Lüers &

Petzel 1958) or not at all (Romatowski, Tolksdorf & Wiedemann 1955).

The nuclear chromatin is characteristically coarse (Burger 1932, Undritz 1933, Harm 1955 a), appearing as clumps with intervening clear spaces (Burger 1932, Undritz & Sepibus 1957, Rind 1958).

The eosinophils show changes similar to those seen in the neutrophils (Rosse & Gurney 1959, Alder 1957), while less noticeable changes are found in the basophils (Rosse & Gurney 1959). The monocytes and lymphocytes have been described as having coarse nuclear chromatin (Rosse & Gurney 1959) and the nuclei of monocytes as being less indented (Undritz 1937 b).

In wet film preparations of blood from individuals with the Pelger anomaly coarse nuclear chromatin has been found in all types of leukocytes (Stobbe 1959 a, Rind 1958).

Areas without granulation in the cytoplasm of the neutrophils, not seen in stained smears, have been found in wet film preparations (Stobbe 1959 a). The cytoplasm has, with few exceptions (Schilling 1933, Plettenberg 1945), been described as showing no abnormalities in stained smears.

In the homozygous form of the Pelger anomaly more than 90 per cent of the neutrophils in stained smears have round nuclei, the remainder being slightly indented (Haverkamp Begemann & van Lookeren Campagne 1951, Stobbe 1959 a). However, in wet films slightly indented nuclei predominate in the neutrophils (Stobbe 1959 a). Undritz & Sepibus (1957) state that very rarely can a bi-segmented nucleus be seen in the neutrophils from individuals with homozygous Pelger anomaly. The eosinophils have only round nuclei, but in the basophils and the monocytes the nuclei are partly indented (Undritz & Sepibus 1957, Stobbe 1959 a). In the stained smears

all types of leukocytes have a coarse nuclear chromatin (Stobbe 1959 a, Alder 1957).

The bone marrow from healthy individuals with the Pelger anomaly shows a normal degree of cellularity. There is usually a relative increase of neutrophilic myelocytes and metamyelocytes (Stahel 1937, Stodtmeister 1936, Undritz 1937 b, Leitner 1943). Coarse nuclear chromatin is visible in promyelocytes and in subsequent stages of the myeloid series of the bone marrow (Undritz 1937 b, Leitner 1943, Rind 1958, Stahel 1937). Also, the nuclear chromatin in the erythroblasts is noticeably coarse (Stobbe 1959 a). Decreased lobulation of the nuclei in megakaryocytes has been described (Undritz 1937 b).

Kokubo (1936, 1939) described a family in which he observed individuals with an increased number of tri-segmented neutrophils that in other respects had the characteristics of the Pelger anomaly. This condition he called "Half-typical Pelger's Anomaly."

Ebbing (1950 b) similarly found in some of the members of a family an increased number of tri-segmented neutrophils, in which the Pelger characteristics were less distinct. This variety was called by Undritz (1959) the "verwässerte" Pelger anomaly.

Petzel & Undritz (1957) described a family in which some of the members had leukocytes with atypical Pelger characteristics which they called "the Stodtmeister type". In the affected individuals about 20 per cent of the neutrophils were of the "Stodtmeister type", and the remaining neutrophils showed typical Pelger characteristics. "The Stodtmeister type" leukocytes have also been compared with pomegranates (Undritz 1959) and called "a flea-like type" (Davidson 1961). The nuclei in the "Stodtmeister type" of neutrophils are indented or almost round with smooth edges, except for some threadlike nuclear projections extending into the cytoplasm.

Neutrophils of the "Stodtmeister type" have been found in all except the first reported case of "the partial form" of the Pelger anomaly (Undritz 1937 a, 1960).

Harm (1955 a) has classified the neutrophilic leukocytes according to nuclear form and chromatin structure in three groups: A-cells (= normal), B-cells (= intermediate) and C-cells (= Pelger leukocytes).

In cases of Pelger anomaly A-cells are not found, but sometimes B-cells. Depending on the relative proportions of unsegmented, bi- and tri-lobed C-cells, Harm divides the heterozygous Pelger anomaly into three types: I, II and III. In type I unsegmented and "dumb-bell" forms predominate. Tri-lobed forms occur occasionally in type II, but more frequently in type III.

The Pelger anomaly and diseases

The anomaly was originally described in two unrelated patients (Pelger 1928). At autopsy one of them was shown to have tuberculosis, while in the other a tuberculous infection was suspected, but could not be confirmed (Huët 1932). It was therefore first suggested (Pelger 1928) that an infection (tuberculosis) had caused similar changes in the leukocytes of both patients (Huët 1932, Schilling 1933).

Stahel (1936) summarized data on the incidence of tuberculosis in some of the families where the Pelger anomaly was first described (Huët 1932, 1931 b, Burger 1932, Undritz 1934, Dietzel 1935, Leitner & van Leeuwen 1935). He found a higher rate of the disease in individuals with the Pelger anomaly as compared with their normal relatives. Accordingly, he assumed that the anomaly eventually predisposed to tuberculosis (Stahel 1936, 1937). Wegmann (1948) described a family in which two sibs, living under similar conditions at the same time, be-

came infected with tuberculosis. The sister who had the Pelger anomaly died, while her normal brother recovered from the disease. Wegmann considered this to indicate that the Pelger anomaly was associated with a lower resistance to tuberculosis.

Soon after the anomaly was discovered, however, families with the Pelger anomaly but without tuberculosis were reported (Jordans 1932, Steinberg & Kanibolotskaja 1935, Peterson 1935, Zündel 1935). Their number successively increased. Nachtsheim (1960) found that the rate of tuberculosis was not higher in the families with the anomaly than in the general population.

Hematologic disorders such as myelogenous leukemia (Huber 1939), acute leukemia, thrombocytopenic purpura (Alder & Schaub 1952), polycythemia vera (Hittmair & Leibetseder 1958, Rado & Hammer 1959), have been described in individuals having the anomaly. Elliptocytosis (Rosse & Gurney 1959), congenital malformations (Degenhardt & Wiedemann 1953, Wegmann 1948, Kase 1961, Podhradsky 1959), frequent abortions (Koelewijn & Keizer 1948, Haverkamp Begemann & van Lookeren Campagne 1951, 1952) allergic manifestations (Leitner & van Leeuwen 1935), diabetes mellitus (Hardon & Blum 1938, Schüttmann 1958, Shipton 1952) and other diseases have also been found in families together with the Pelger anomaly. Sufficient evidence for a causal association of the anomaly with any of these conditions has not been found.

Neurologic and mental disorders or mental deficiency have been reported in individuals with the Pelger anomaly (Klein, Hussar & Bornstein 1955, Huët 1931 b, Lorentz 1937, Plum 1953, Plettenberg 1945). In the family described by Haverkamp Begemann & van Lookeren Campagne (1952) an individual homozygous for the Pelger anomaly and some of the heterozygous relatives suffered from epilepsy. Schilling 1952) interpreted this as sufficient evidence of a harmful effect of the

Pelger gene, which could become manifest even in the heterozygote as a neurologic or mental disorder.

Riebeling (1952) stated that the anomaly occurred more frequently in people with mental disorders than in the normal population. Subsequent studies on the frequency of the anomaly (Ebbing 1959 a, 1959 b, Redies, Quenzer, Tolksdorf, Saile & Wiedemann 1958, Wiedemann & Saile 1957) have not confirmed this statement. Nachtsheim (1960) has shown that the frequency of the Pelger anomaly in people with mental disorders is not higher than in the general population. This has been confirmed by other investigators (Ludden & Harvey 1962), who found no apparent relation to specific illnesses or a predisposition to infection.

Function and biological properties of the leukocytes with the Pelger features

Repeated observations have shown that individuals hetero- or homozygous for the Pelger anomaly react to acute generalized and localized infections in the same way as normal individuals (Huët 1932, Dietzel 1935, Roos 1936, Davidsson, Lawler & Ackerley 1954, Stobbe 1959 b). Those heterozygous for the anomaly also react like normal persons to attacks of hyperthermia produced by unspecific pyrogenic agents and to local irritants such as cantharides and turpentine (Zündel 1936, Stahel 1936, Hadorn & Blum 1938).

In certain infections neutrophilic myelocytes may occur in appreciable numbers in the blood, and the blood picture resembles that of a homozygous Pelger anomaly (Lüers, Nachtsheim & Petzel 1956). Similar changes have been provoked through injections of colchicine into rabbits (Harm 1953).

Adorf (1953) and Rosse & Gurney (1959) infused blood from normal individuals into recipients having the Pelger anomaly

and blood from individuals with the anomaly into normal recipients, and studied the rate of disappearance of the neutrophils from the peripheral blood. Most of the foreign neutrophils disappeared from the blood of the recipients in a few hours. The rate of disappearance was found be the same for normal and Pelger neutrophils, and to agree well with results obtained by other methods, when using normal leukocytes and normal recipients.

The phagocytic activity of leukocytes with Pelger characteristics does not differ from that of normal leukocytes (Terhorst 1957, Stobbe 1959 a). Leitner and Gugelot (1938) found marked phagocytic activity in mature Pelger neutrophils, but less in immature ones. Adorf (1953) infused blood from persons heterozygous for the Pelger anomaly into normal recipients and found no difference between the phagocytic activity of the two kinds of leukocytes.

Kokubo (1936, 1939) found no difference in the peroxidase activity of normal leukocytes and those with the Pelger characteristics. This was confirmed by Tempka, Hanicki & Uransinski (1961), who also found normal amounts of lipid and glycogen in the Pelger leukocytes. On the other hand, they state that in the leukocytes from individuals with the Pelger anomaly the DNA content is increased and the alkaline phosphatase activity absent.

Distribution and frequency

Up to 1953 approximately 160 families with several hundred individuals with the Pelger anomaly had been reported (Undritz 1960). The Pelger anomaly has mainly been reported in Europeans (Caucasians), but also in Orientals (Kokubo 1936, 1939, Yamasawa, Fujii & Tsuchitori 1953), American Negroes (Rosse & Gurney 1959) and American Indians (Vianna 1951).

It has thus been shown that the anomaly is not confined to any particular race.

Outside the Netherlands the Pelger anomaly was first reported in Germany and Czechoslovakia (Schilling 1933) and in Switzerland (Undritz 1933, 1934). Soon thereafter it was reported in Russia (Steinberg & Kanibolotskaja 1935) and in France (Chevallier & Ély 1936) and later in other European countries such as Spain (Dominguez Rodino 1947), Sweden (Jonson, Boström & Bringel 1947, 1948), Austria (Steffen & Heeger 1952), Italy (Gramiccia 1946), Poland (Lawkowicz & Wlodarski 1950), Denmark (Plum 1953), Norway (Jorde 1953), England (Davidson, Lawler & Ackerly 1954), Rumania (Ciplea & Ciorapciu 1958), Belgium (Sokal & Levecq 1959), Hungary (Rado & Hammer 1959), Finland (Heinivaara & Kaipainen 1961) and Iceland (Jensson 1962).

Outside Europe the anomaly has been reported in the U. S. A. (Peterson 1935), Java (den Hartog Jäger 1936), Japan (Kokubo 1936), Cuba (Chediak & Bidor 1939), Israel (Nelken 1944), Brazil (De Mendonca 1950), Algeria (Bernard, Undritz, Bru, Mathé & Toulouse 1956) and Australia (Shipton 1952). This list of countries where the Pelger anomaly has been found is not claimed to be complete, but it clearly illustrates the worldwide distribution of the anomaly.

The frequency of the Pelger anomaly was estimated to be about 1 per thousand in Finland (Heinivaara & Kaipainen 1961). In England, in an examination of 36,000 blood smears, six unrelated persons with Pelger anomaly were found, or an incidence of 1:6,000 (Davidson, Lawler & Ackerley 1954). In the U. S. A. an incidence of 1:4,800 was found in an examination of about 3,500 blood films (Skendzel & Hoffman 1962) and an examination of 43,000 persons revealed an incidence of about 1:10,000 (Ludden & Harvey 1962). In Japan (Handa 1959) a frequency of 1 per 1,500 among school-

children has been reported. Some frequency investigations have been carried out in Germany. In Berlin 22,648 inhabitants of all ages and classes were examined and the Pelger anomaly recognized in 18 persons (Nachtsheim 1950 b). In Krefeld examination of 15,097 school-children revealed the anomaly in three of them (Wiedemann & Saile 1957). Out of 12,086 schoolboys from Münster/Westf. three were found to have the Pelger anomaly (Ebbing 1959 a).

The frequency of the anomaly in Germany thus varied from 0.2 to 0.8 per thousand. There is, however, no clear evidence of significant differences in frequency between different parts of the country (Nachtsheim 1960).

In mentally deficient people in Germany frequencies up to 0.8 per thousand were found (Wiedemann & Saile 1957, Ebbing 1959 b, Nachtsheim 1960).

"Acquired Pelger anomaly"

In various diseases reversible Pelger-like changes may occur in the neutrophilic granulocytes. These acquired Pelger-like changes differ from the true Pelger anomaly in that the nuclear chromatin structure is less coarse (Stobbe 1959 b, Davidson 1961). The acquired changes may resemble homozygous or heterozygous Pelger anomaly, but usually only a certain proportion of the granulocytes becomes affected (Stobbe 1959 b, Lüers, Nachtsheim & Petzel 1956).

The acquired Pelger-like changes have been observed in acute enteritis (Heckner 1948), malaria (Undritz 1954), myelogenous leukemia (Baltzer 1953, Darte, Dacie & McSorley 1954, Dorr & Moloney 1959, Shanbrom, Collins & Miller 1960, Heinivaara & Kaipainen 1961, 1962), lymphatic leukemia (Shanbrom, Collins & Miller 1960, Heinivaara & Kaipainen 1961), acute leukemia (Darte, Dacie & McSorley 1954, Pusic & Theo-

dori 1957), aleukemic leukemia (Heinivaara & Kaipainen 1961), myeloma (Böttner & Reinecke 1955, Dorr & Moloney 1959), lupus erythematosus (Walter & Stutz 1961), myxedema (Shanbrom & Tanaka 1962) and during a viral infection (Grosser 1962). The acquired Pelger changes develop late in the course of leukemias. In a patient with acute leukemia the Pelger-like changes were reversible.

Pusic & Theodori (1957) studied leukocytes with acquired Pelger-like changes by histochemical methods and found normal peroxidase activity, lipid and RNA contents in the cells. Dorr & Moloney (1959) found normal peroxidase and alkaline phosphatase activities in leukocytes with acquired Pelger-like changes.

PROBLEMS

In the present study of the Pelger anomaly the following problems have been considered:

1. The genetic control of the Pelger anomaly.
2. Epidemiological aspects and frequency variations of the Pelger anomaly.
3. Cytological and functional aspects of leukocytes with the Pelger characteristics as compared with normal leukocytes.

MATERIAL AND METHODS

The collection of data

For this investigation blood films were examined from about 19,500 inhabitants in Västerbotten County in North Sweden (fig. 1). The blood films were obtained from the following five groups of people:

A. In- and out-patients at Umeå Hospital, the Royal Medical School, Umeå.
B. Blood donors of The Blood Transfusion Service at Umeå Hospital.
C. Army recruits from Västerbotten County.
D. Schoolchildren, 13 to 14 years of age, from three different communities in Västerbotten County.
E. Relatives of the probands in groups A—D.

The blood films were made in the usual way on microscope slides, dried in air, fixed in methanol and stained with a Romanovsky staining method.

Group A consists of all the patients, *i.e.* full admissions as well as those using the out-patient services at Umeå Hospital during the period 1957 to 1960 inclusive, from whom routine blood films were taken. Furthermore, this group also includes a few patients whose blood films were sent from different parts of the county to Umeå Hospital for examination. About 15,000 patients were examined.

All the routine blood films were subjected to a differential leukocyte count carried out in the Department of Clinical Chemistry at Umeå Hospital.

The technicians were instructed to save for closer study all

Fig. 1. Map showing the location of Västerbotten County (hatched area).

blood smears with leukocytes showing nuclear changes suggesting the presence of the Pelger anomaly. These blood films were examined by myself.

Fig. 2. Map showing the distribution according to the residence of patients in the Department of Internal Medicine of Umeå Hospital during the years 1957—1959 (Patients per thousand inhabitants of the communities).

As a rule Umea Hospital accepts patients from the southern coastal districts and the inland part of Västerbotten County. This is shown by the fact, that during 1957—1959, 95.2 per cent of the patients of the Department of Internal Medicine came from that part of the county (cf. fig. 2). 2.9 per cent (216) lived in the nothern coastal districts, while 1.9 per cent (134) resided outside the county.

In *group B* there are 1,614 blood donors, from whom blood films were obtained at their first visit for the giving of blood

at the Blood Transfusion Service at Umeå Hospital during the period July 1958 to the end of 1959. The blood donors represented both sexes and their age varied between 18 and 60 years. Only blood donors residing in Västerbotten County are included in this investigation. Many of them (students, seasonal workers etc.) lived temporarily in Umeå and the surroundings, while their domiciles were spread throughout the county. All army recruits who gave blood at Umeå Hospital during the actual period of time are excluded from this group.

Group C comprises 1,598 army recruits. Their blood smears were collected in 1959 and 1960 in connection with routine examinations for military service. The majority of them were between 19 and 21 years of age. They came from every community in Västerbotten County.

Group D consists of 308 schoolchildren, 13 to 14 years of age, from three different communities, *i. e.* Bygdeå and Holmsund Communities and Umeå Rural Community (they are shown in fig. 2 by the figures: 12.8, 20.7 and 17.5 per thousand respectively).

Group E comprises all examined relatives (about 1,000) of the individuals with the Pelger anomaly *i. e.* the probands who were discovered at the examination of groups A —D. The collection of blood films from the relatives began late in 1958 and continued until the beginning of 1961. It was based on the information obtainable from the probands and their relatives.

By the examination of the blood films from the patient population of Umeå Hospital (group A) 88 individuals were found to have the Pelger anomaly. In the Department of Internal Medicine 50 patients with the Pelger anomaly were discovered, while 38 patients were found in the other departments and the out-patients services of the hospital (cf. table 1).

The examination of blood films from the individuals in

groups B–D revealed the presence of the Pelger anomaly in 10 individuals, *i.e.* 4 blood donors, 4 army recruits and 2 schoolchildren. One of the individuals, who in 1958 had been an inpatient in the Department of Internal Medicine and then found to have the Pelger anomaly, was later registered for the second time among the blood donors.

Thus, a total number of 97 probands was obtained by examination of blood films from all the individuals in the four groups A–D.

In the fifth group (E) comprising the examined relatives of the 97 probands, 228 relatives were found to have the Pelger anomaly. Accordingly, in this investigation, the anomaly was discovered in 325 individuals. In many of the individuals the diagnosis of the Pelger anomaly was repeatedly confirmed through the examination of new blood films.

The blood films from the relatives were mainly obtained through personal visits to the homes. Others were obtained in cooperation with neighbouring physicians or district nurses, and from some of the relatives the films were made at Umeå Hospital. The relatives usually lived in Västerbotten County.

All the blood films from groups B—E were carefully scrutinized by a trained technician and subsequently checked by myself.

TABLE 1. *The probands of the patient population of Umeå Hospital and its out-patients services by year the Pelger anomaly was diagnosed.*

Department	Number of probands by year				Total
	1957	1958	1959	1960	
Dept. of Int. Medicine.	20	16	8	6	50
Other dept.	9	11	12	6	38

Techniques used in the examination of leukocytes

The morphologic features of the leukocytes were studied in blood films stained by a Romanovsky staining method. Differential leukocyte counts and counts of nuclear drumsticks were carried out in such stained smears.

For the demonstration of the peroxidase activity in the leukocytes, either the technique of Graham-Knoll (Undritz 1952) or that of Sato, Suzuki & Shibata (1934) was used.

The alkaline phosphatase activity was estimated in the leukocytes by the semiquantitative cytochemical technique described by Merker & Heilmeyer (1960).

Tests of phagocytic activity were performed on leukocytes separated from venous blood.

For chromosome studies leukocytes obtained from either venous blood or bone marrow were cultured according to the method described by Moorhead, Nowell, Mellman, Battips & Hungerford (1960). Somewhat altered, this technique was used in experiments on the incorporation of H^3-thymidine into bone marrow cells.

The separation of leukocytes from venous blood was carried out according to the method described by Skoog & Beck (1956). Dextran with a high molecular weight (Mw = 153,000) was used to agglutinate and to increase the sedimentation rate of the erythrocytes.

Venous blood (approximately 6 ml) was collected directly into a sterile 3 per cent solution (approximately 3 ml) of dextran in saline. A 5 per cent solution of heparin without a preservative was used as an anticoagulant. The blood was thoroughly mixed with the dextran solution and then left standing undisturbed to allow the erythrocytes to sediment. After about 30 minutes the erythrocytes were sedimented, while the leukocytes still were suspended in the supernatant plasma.

The leukocyte suspension was then transferred gently by

aspiration to a new sterile test tube, and a leukocyte count of an aliquot was determined in a counting chamber.

For chromosome analyses and experiments on H^3-thymidine incorporation, cell suspensions containing 1,000 leukocytes per cmm were made by the addition of suitable quantities of culture medium. In the experiments on bacterial phagocytosis leukocyte suspensions of 10,000 leukocytes per cmm were made. All centrifugations in connection with the leukocyte experiments were carried out at about 600 r. p. m. for 10 minutes.

Diagnosis of the Pelger anomaly

In the blood films the Pelger characteristics were easily recognized in the neutrophils (fig. 3) and even in the eosinophils. Similar nuclear characteristics in the other blood cells were not definitely seen.

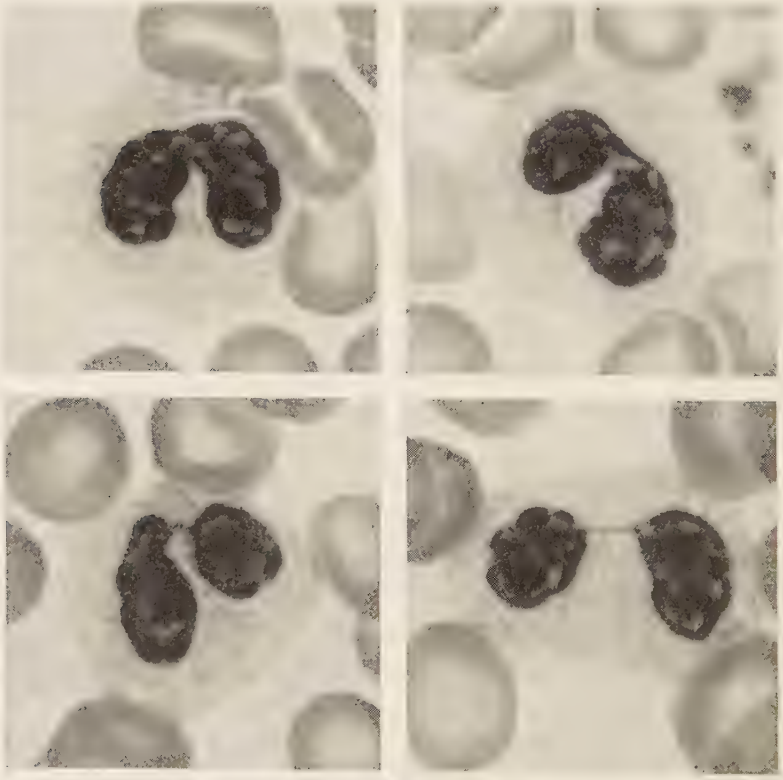

Fig. 3. Pelger neutrophils at different stages of segmentation.

TABLE 2. *Mean of differential leukocyte counts (per cent) in blood films from 52 individuals with the Pelger anomaly and 21 normal individuals.*

	Neutrophils		Eosino-	Baso-	Lympho-	Mono-	Total
	Unsegm.	Segm.	phils	phils	cytes	cytes	
Normal	5.1	51.6	2.8	0.3	34.8	5.4	100
Pelger	33.2	22.8	3.0	0.1	37.5	3.4	100

TABLE 3. *Mean percentage distribution by number of nuclear lobes in neutrophils from 52 individuals with the Pelger anomaly and 21 normal individuals.*

	Number of nuclear lobes					Total
	1	2	3	4	5	
Normal	8.9	21.1	49.7	19.4	0.8	100
Pelger	59.3	40.2	0.5	—	—	100

The only characteristic finding in the bone marrow of healthy individuals with the Pelger anomaly was a slight predominance of neutrophilic myelocytes and mature neutrophils. The earliest state in which the Pelger characteristics could be observed was in the neutrophilic myelocytes.

Although not essential for the diagnosis of the Pelger anomaly differential leukocyte counts were made in the blood films from the majority of the individuals who had the Pelger anomaly. Table 2 shows the results of differential leukocyte counts in healthy individuals with the anomaly and over 15 years of age. The distribution of nuclear lobes of the Pelger neutrophils (mean 1.4) as compared to normal neutrophils (mean 2.8) is shown in table 3.

Nuclear forms described as typical for the leukocytes of homozygotes were not seen.

The Pelger anomaly is easily recognized in blood films and also in bone marrow films. However, in patients with reactive

changes in the myelopoiesis the anomaly may be overlooked in the bone marrow and difficult to recognize in blood films. The Pelger anomaly was, in this investigation, distinguished without difficulty from "the acquired form of the anomaly." The percentage of Pelger-like neutrophils was usually low in individuals with the acquired form, and, if high, as was occasionally seen in severe infections, the changes were transient and disappeared on recovery. Typical nuclear chromatin changes never did occur in the Pelger-like leukocytes.

The nuclear sex of neutrophils with Pelger characteristics

The sex chromatin is a small mass of heterochromatin detectable in a varying proportion (usually in 40—60 per cent) of the interphase nuclei of female cells in man and some other animals (Böök & Santesson 1962). This sexual dimorphism of the cell nuclei was discovered in 1949 by Barr & Bertram in nerve cells of cats. Davidson & Smith (1954) discovered another sexual dimorphism, in the nuclei of the neutrophils of the peripheral blood. In a proportion (1—10 per cent) of these neutrophils a small accessory lobe called a drumstick occurs in females, but very rarely, if at all, in normal males.

Observed in the microscope the typical drumstick has a round head with a diameter of about 1.5 μ. It stains as densely as the rest of the nucleus to which it is attached by a fine filament of chromatin. Sometimes it is difficult to distinguish the drumsticks from other types of nuclear chromatin protrusions such as "sessile nodules", "small clubs" and "racket forms" (Davidson & Smith 1954).

Cytogenetical tests based on the presence or absence of sex chromatin in somatic cells and drumsticks in the neutrophils of the peripheral blood have now become important aids in the diagnosis of abnormalities of sexual development.

Davidson & Smith (1954) found an average of 2.6 per cent of normal female neutrophils to have drumsticks. Similarly, Romatowski, Tolksdorf & Wiedemann (1955) found drumsticks in 2.3 per cent of normal female neutrophils. On the other hand, in the neutrophils of women heterozygous for the Pelger anomaly drumsticks have either not been found (Romatowski, Tolksdorf & Wiedemann 1955, Etscheverry 1962, Skendzel & Hoffman 1962) or have been found with a low frequency (Davidson 1962). Lüers & Petzel (1958) observed drumsticks with a frequency up to 1.2 per cent in the neutrophils from 12 out of 20 females with the Pelger anomaly.

In this investigation drumsticks have been counted in the neutrophils from normal females and females with the Pelger anomaly of three different pedigrees (cf. Appendix, pedigrees 1, 6 and 15). In 500 neutrophils from each of the females typical drumsticks and other nuclear appendages were counted separately (table 4). The other nuclear appendages in the neutrophils from the females with the anomaly were mainly minute prostrusions of nuclear chromatin, sometimes with an appearance of "small clubs." In 15 females with the Pelger anomaly the frequency of typical drumsticks varied between zero and 0.8 per cent in the neutrophils (average of 0.4 per cent). In 15 normal females drumsticks occurred with a frequency varying between 1.2 and 3.6 per cent (average 2.5 per cent).

The frequencies for normal females agree with those reported by previous investigators. On the other hand, in this material the drumsticks apparently occurred more regularly in females with the Pelger anomaly as compared to previous series (Lüers & Petzel 1958, Davidson & Smith 1954, Davidson 1961). However, the results are similar to those reported by Lüers & Petzel (1958).

TABLE 4. *The occurrence of sex specific drumsticks in Pelger and normal neutrophils. Counts of 500 neutrophils from each person examined.*

Pedigree	Number of individuals in pedigree	Drumsticks per 500 neutrophils		Other nuclear protrusion 500 neutrophils	
		Pelger	Normal	Pelger	Normal
1	V. 55	2		4	
	V. 59	1		4	
	V. 68	2		7	
	V. 70	2		13	
	V. 71	3		8	
	V. 72		11		14
	V. 74	2		7	
	VI. 70	4		4	
	VI. 71		18		18
	VI. 72		11		13
	VI. 73		6		5
	VI. 75	0		4	
	VI. 80		12		11
	VI. 83		14		18
	VI. 84		15		24
	VI. 86		9		16
	VI. 87	3		5	
	VI. 93		16		18
	VII. 98		12		12
	VII. 100		13		14
	VII. 104	2		5	
6	III. 2	2		9	
	III. 3		13		17
	III. 14	1		4	
	III. 16		11		18
	IV. 2		14		17
	IV. 3		9		18
	IV. 17	2		2	
	IV. 18	1		4	
15	II. 2	2		14	

Chromosome studies

One of the most interesting recent developments in the field of human cytogenetics has been the discovery of a number of chromosomal aberrations associated with different pathological conditions. Thus, the presence of an additional small chromosome—*i. e.* trisomy of no. 21 (Denver classification)—is typical in cases of mongolism (Lejeune, Gautier and Turpin 1959, Böök, Fraccaro & Lindsten 1959). A decreased mean lobe count in the neutrophils has been described in mongolism (Turpin & Bernyer 1947, Shapiro 1949, Mittwoch 1958) and also an increased incidence of leukemia (Stewart, Webb & Hewitt 1958).

It is possible that the additional chromosome occurring in mongolism affects leukopoiesis. A characteristic abnormal chromosome probably derived from one of the small chromosomes (no. 21 or 22) is commonly found in chronic myeloid leukemia, and it has been postulated that the same chromosome is involved in chronic myeloid leukemia as in mongolism (Tough, Court Brown, Baikie, Buckton, Harnden, Jacobs, King & McBride 1961, Nowell & Hungerford 1960). The significance of these findings is still unclear, but they seem to indicate that cytogenetic studies in human leukocyte anomalies might give valuable information.

In the present investigation chromosomes have been studied in short term cultures of blood and bone marrow cells from individuals with the Pelger anomaly. The technique described by Moorhead, Nowell, Mellman, Battips & Hungerford (1960) has been used, but with minor modifications.

When bone marrow was used it was aspirated and immediately mixed with culture medium containing heparin. Cultures of 10 ml were then set up, but without adding phytohemagglutinin. The bone marrow cells were incubated for 24 hours, but exposed to colchicine and otherwise treated and

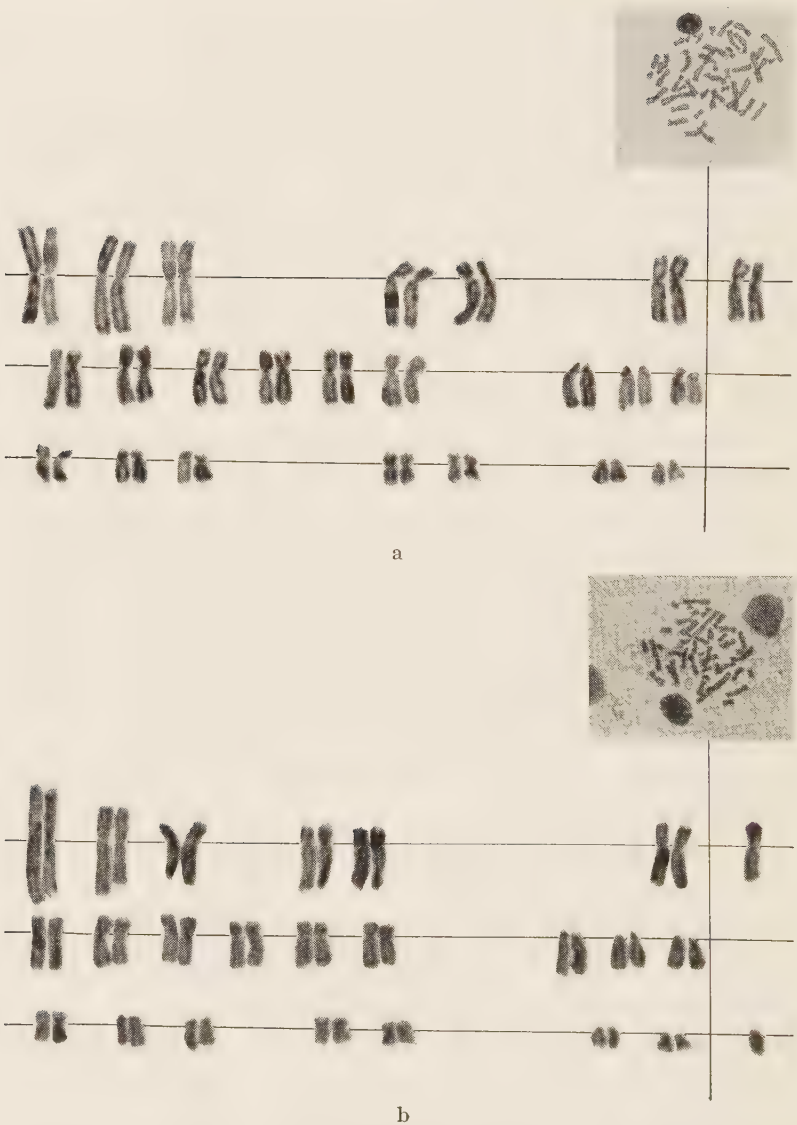

Fig. 4. The karyotype of mitotic metaphase chromosomes obtained from cultures of leukocytes from peripheral blood of individuals with the Pelger anomaly, (a) a female, (b) a male.

TABLE 5. *Chromosome counts in four different individuals with the heterozygous form of the Pelger anomaly.*

The individuals number in pedigrees	Sex	Tissue	Chromosome counts 45	46	47	Total cells
9, III. 7	F	Bone marrow		12		12
15, II. 2	F	„ „	2	10	1	13
1, VI. 70	F	Blood cells	4	19		23
2, IV. 52	F	„ „		14		14
9, III. 7	F	„ „	1	11		12

prepared in the same way as the leukocytes cultured from venous blood.

Chromosome counts were only carried out in apparently undamaged cells in which the chromosomes could be clearly distinguished. Counts deviating from 46, which is the normal chromosome number in man, are explained by unavoidable technical errors (table 5). Detailed analyses of the karyotypes of these individuals, as shown in fig. 4, revealed apparently normal diploid sets of chromosomes both in males and females.

CERTAIN BIOLOGICAL AND BIOCHEMICAL PROPERTIES OF THE LEUKOCYTES WITH PELGER CHARACTERISTICS AS COMPARED WITH THOSE OF NORMAL LEUKOCYTES

For the understanding of possible biological advantages or disadvantages associated with the Pelger anomaly it might be important to know whether differences in biochemical and biological properties between normal leukocytes and those with Pelger characteristics can be found.

In some of the reports on the Pelger anomaly such differences have been claimed to exist. Thus, Tempka, Hanicki & Uransinski (1961) found no alkaline phosphatase activity in the leukocytes from individuals with the Pelger anomaly. They also claimed that the DNA content of these leukocytes is increased as compared to normal leukocytes. Other investigators (Leitner & Gugelot 1938) have found the phagocytic activity of leukocytes with the Pelger characteristics to be less than that of normal leukocytes.

The alkaline phosphatase and the peroxidase activity

Changes in the alkaline phosphatase activity of mature neutrophils have been reported to occur in several diseases (Merker & Heilmeyer 1960). Infectious diseases, aplastic anemia, polycythemia vera and some other diseases of the hematopoietic system may cause an increase in the leukocyte alkaline phosphatase activity. In chronic myelogenous leukemia the alkaline phosphatase activity of the neutrophils is greatly reduced or absent.

TABLE 6. *Alkaline leukocyte phosphatase activity in individuals with the Pelger anomaly.*

Case no	Positive granulocytes per cent	Leukocyte alkaline phosphatase scores
1	75	102
2	45	59
3	32	41
4	21	28
5	80	138
6	50	68
7	76	144
8	78	140
9	44	63
10	72	108
11	45	54
12	67	106
13	54	72
14	41	59
15	33	43
16	55	81
17	28	38
18	84	140

In the present investigation the alkaline phosphatase activity has been examined in the neutrophils from 18 individuals with the Pelger anomaly of both sexes and of different ages.

The semiquantitative cytochemical technique described by Merker and Heilmyer (1960) was used. Only new and thin blood films were used for the measurement of the phosphatase activity. For this purpose a total number of 100 neutrophils from each individual was surveyed. Cells showing alkaline phosphatase activity were grouped into 5 classes graded from 1 to 5. Cells with no activity were designated zero. The alkaline

phosphatase activity is expressed by the sum of the score numbers per 100 neutrophils (normal range 20—100).

The level of alkaline phosphatase activity was found to be normal in 11 and somewhat elevated in seven of the individuals examined (table 6). The increase in the alkaline phosphatase activity may have been caused by undetected minor infections.

The results obtained do not agree with those of Tempka, Hanicki & Uransinski (1961), who were unable to demonstrate any alkaline phosphatase activity in Pelger neutrophils.

During the collection of this material the peroxidase activity of Pelger leukocytes has been repeatedly tested, either with the technique of Graham-Knoll (Undritz 1952) or that of Sato, Suzuki & Shibata (1934). In the present study the peroxidase activity of the Pelger leukocytes was similar to that of normal leukocytes. The findings are in good agreement with those of other investigators (Kokubo 1936, 1939, Terhorst 1957, Tempka, Hanicki & Uransinski 1961).

Phagocytic activity

Leitner & Gugelot (1938) tested the phagocytic activity of leukocytes from individuals with the Pelger anomaly and found that it was decreased in the immature neutrophils. Hence, they concluded that individuals with the anomaly might be less resistent to severe infections than individuals not having the anomaly.

These results, though often cited by different authors, have not been confirmed by later investigators (Terhorst 1957, Stobbe 1959 a). Only Terhorst (1957) gives in detail results of experiments which showed no difference in the phagocytic activity between the two types of neutrophils.

In the present investigation the phagocytic activity of both kinds of leukocytes has been compared *in vitro*.

TABLE 7. *Phagocytic activity of leukocytes from individuals with the Pelger anomaly and normal individuals.*

Phenotype and case no.	Percentage of phagocytizing granulocytes	Mean number of cocci phagocytized per granulocyte	Percentage of phagocytizing lympho- and monocytes	Mean number of cocci phagocytized per monocytoid cell
Pelger:				
1	41.6	5.0	4.3	2.5
2	15.2	3.8	4.3	2.6
3	18.9	5.1	7.6	5.3
4	26.4	4.5	2.3	1.6
5	21.2	3.1	7.0	3.4
6	24.8	3.3	3.3	3.3
7	13.1	3.4	2.6	1.8
8	9.4	3.4	2.0	2.3
9	25.3	6.6	1.0	3.3
Mean:	21.8	4.2	3.8	2.9
Normal:				
1	43.5	5.1	6.3	4.2
2	15.7	3.5	1.3	1.5
3	29.5	4.5	3.6	4.0
4	16.8	4.2	2.3	3.6
5	14.2	3.0	1.6	1.8
6	9.5	5.2	1.0	1.3
7	6.8	3.8	1.6	1.8
8	15.7	4.6	4.0	3.8
Mean:	19.0	4.2	2.7	2.7

Leukocytes were separated from venous blood of healthy individuals. The concentration of the leukocytes in the specimens was determined and after centrifugation adjusted to 10,000 cells per cmm by drawing off an appropriate amount of the supernatant plasma.

The bacterium used was a strain of *staphylococcus aureus*, type 209, purchased from Statens bakteriologiska laboratorium in Stockholm. The staphylococci were obtained from a 24-hour blood-agar culture in saline suspension made to contain about 25,000 bacteria per cmm.

The test was carried out by mixing 0.5 ml of leukocyte and 0.2 ml of bacterial suspensions in a sterile test tube, and incubating the mixture at 37° C for 60 minutes. After the incubation, smears of the leukocyte suspension were made on microscope slides with the same technique as used in making blood films. The smears were dried in air, fixed for 10 to 15 minutes in methanol and stained with a Romanovsky staining method.

The phagocytic leukocytes were easily recognized and in most of them the number of phagocytized cocci could be counted without difficulty.

From each individual a total number of 1,000 neutrophils was examined. The percentage of phagocytic neutrophils and the number of phagocytized cocci was determined. 300 lymphocytes and monocytes were similarly examined.

The results are shown in table 7. There is a pronounced variation in the phagocytic activity of the leukocytes from different persons, whether they have the Pelger anomaly or not.

There was no significant difference between the phagocytic activity of the leukocytes from individuals with the Pelger anomaly and the leukocytes from individuals not having the anomaly.

Experiments on the incorporation of H^3-thymidine into bone marrow cells

Abnormalities in the synthesis of deoxyribonucleic acid (DNA) in bone marrow cells as measured by isotope techniques *in vitro* have been reported in certain diseases (Cronkite, Bond, Fliedner & Killman 1960, Craddock 1960, Alfrey, Kiely, Tauxe & Owen 1961).

In the present investigation an attempt has been made to compare the *in vitro* production of DNA in bone marrow cells from individuals with the Pelger anomaly and normal persons. The cells were incubated with H^3-thymidine, which was used to label the DNA synthesized in them during a specific period of time. By means of autoradiography the DNA production in the cells was estimated semiquantitatively.

Thymidine is a specific precursor of DNA utilized in its formation in growing cells (Reichard & Estborn 1951, Friedkin, Tilson & Roberts 1956). By using thymidine labelled with tritium autoradiograms with high resolution are obtained owing to the low energy (0.019 MeV) of the beta particles emitted by the tritium (Lajtha 1961).

For the present experiments bone marrow cells were obtained from healthy Pelger and normal individuals. All of them had normal white-cell counts as well as normal hemoglobin and erythrocyte sedimentation rates. Tests for c-reactive protein were negative. Tests for glucose and protein in the urine were also negative. Stained blood and bone marrow films showed no pathologic changes.

Bone marrow obtained by sternal puncture was immediately mixed with culture medium. The concentration of nucleated cells was adjusted to about 1.0×10^6 per ml. Thereafter 0.25 μC of H^3-thymidine (specific activity 2 mC/mM) was added per ml of culture medium. The cell suspension was then distributed in 5 ml portions into sterile bottles, which were incubated at

37° C for periods of 4, 8 and 24 hours. To ensure uniformity in the experiments the same batch of culture medium was used in all the series of incubations with H^3-thymidine.

At the end of each incubation period a sample of incubated cells (preferably the contents of one bottle) was treated and prepared according to the technique used for leukocytes cultured from blood for chromosome studies as described by Moorhead, Nowell, Mellman, Battips & Hungerford (1960). A second sample of incubated cells was treated similarly except that the cells, instead of being exposed to hypotonic Hanks solution for 10 minutes, were suspended and kept for the same length of time in 10 per cent acetic acid.

After fixation of the cells in methanol and glacial acetic acid slides were prepared by air drying and stained in aceto-orcein according to the method of Moorhead, Nowell, Mellman, Battips & Hungerford (1960).

Autoradiograms of the stained cells were made by dipping the slides into a melted, warm (45° C) Eastman Kodak NTB_3 emulsion. The emulsion was dried by hanging the slides overnight in a dark room. When completely dry the preparations were placed into light-tight boxes with desiccant and kept at +4° C for an exposure time of 10 days. The autoradiograms were then developed at a temperature of 20° C in the conventional way using a developing time of 4 minutes in an Eastman Kodak developer ("Dolmi").

The quantity of DNA produced in the cells during the incubation periods was estimated by evaluating the degree of labelling of the cells with H^3-thymidine as shown by the number of grains produced in the autoradiogram over the cells.

This semiquantitative measurement of the DNA was based on a study of 200 cells in each incubated sample. No attempts were made to differentiate cells other than by their degree of labelling. The cells were grouped into 8 classes scored from

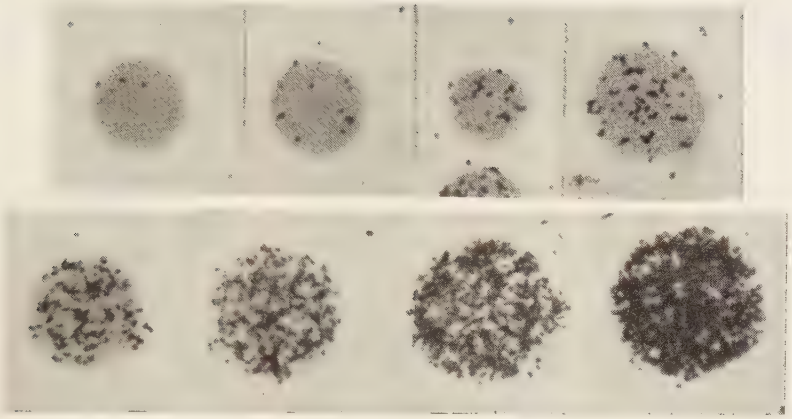

Fig. 5. Bone marrow cells showing different degrees of labelling with H^3-thymidine.

0—7 (fig. 5). Cells with less than 4 grains were regarded as unlabelled (score number = 0), and those having score numbers of 4 or more were designated as heavily labelled. The total score per 200 cells and the percentage number of heavily labelled cells have been used as measures of the production of DNA over the specific incubation periods.

In table 8 are shown the results of experiments, where duplicates of bone marrow samples from two Pelger individuals were incubated for periods of 4, 8 and 24 hours.

In acetic acid the DNA is insoluble and not lost from the cells. Tables 9 and 10 show that the same results were obtained when the incubated cells were treated with hypotonic Hanks solution as with 10 per cent acetic acid. Consequently one may assume that no DNA was lost during the treatment with the hypotonic solution.

In general the number of cells labelled with H^3-thymidine increased with the time of incubation. The quantity of incorporated H^3-thymidine, i. e. the degree of labelling of individual cells, usually increased with the time of incubation (table 10).

TABLE 8. *The incorporation of H^3-thymidine into bone marrow cells from two Pelger individuals as measured by autoradiography. The bone marrow samples were incubated in duplicate.*

Case no.	Measurement	Number of cells labelled per 200 cells (incubation period, hours)			Percentage of heavily labelled cells (incubation period, hours)		
		4	8	24	4	8	24
I	1	26	45	36	4	49	75
	2	26	39	36	8	51	66
III	1	29	45	45	18	47	64
	2	32	39	50	16	54	66

TABLE 9. *The number of cells labelled with H^3-thymidine (per 200 cells) in relation to time of incubation and the treatment of cells following incubation.*

Phenotype and case no.	Cells treated with hypotonic Hanks solution (incubation period, hours)			Cells treated with acetic acid (incubation period, hours)		
	4	8	24	4	8	24
Pelger:						
1	26	45	36	34	35	36
2	*	*	*	20	20	30
3	32	39	50	**	**	**
4	34	42	47	29	38	49
5	30	27	59	35	37	53
6	17	32	57	17	35	49
Normal:						
1	18	51	61	23	50	56
2	27	39	61	34	41	45
3	25	31	56	26	27	47
4	38	53	47	40	48	59
5	23	28	44	27	24	41
6	30	32	45	33	37	45
7	35	42	49	*	37	51

*) Figures missing due to experimental failure.

**) Treatment with acetic acid omitted due to lack of cells.

TABLE 10. *The percentage of heavily labelled cells in relation to time of incubation and the treatment of cells following incubation.*

Phenotype and case no.	Cells treated with hypotonic Hanks solution (incubation period, hours)			Cells treated with acetic acid (incubation period, hours)		
	4	8	24	4	8	24
Pelger:						
1	8	49	75	3	54	75
2	*	*	*	15	50	50
3	16	54	66	**	**	**
4	26	64	79	31	58	76
5	17	70	68	23	60	74
6	6	41	60	12	37	65
Normal:						
1	33	77	71	31	76	79
2	30	66	74	38	68	76
3	60	74	84	46	70	81
4	24	55	69	30	56	70
5	56	78	79	30	75	73
6	17	44	64	30	48	60
7	23	49	57	*	59	67

*) Figures missing due to experimental failure.
**) Treatment with acetic acid omitted due to lack of cells.

However, in most instances a great deal or even the majority of cells labelled over a 24-hour period apparently had begun to incorporate H^3-thymidine during the first 4 hours of incubation (table 9). There was, however, a considerable variation between the results obtained with cells from different individuals. The most pronounced individual variation in the percentage of heavily labelled cells was observed after four hours, while it was found to be less after longer periods of incubation.

No significant difference in DNA production as measured by the uptake of H^3-thymidine into the cells could be detected between the bone marrow cells from the individuals with the Pelger anomaly and those from normal individuals.

PATHOLOGIC LEUKOCYTE CHANGES IN PATIENTS WITH THE PELGER ANOMALY

Neutrophilic leukocytosis more than 10,000 cells per cmm was repeatedly observed in patients with the Pelger anomaly who were afflicted with diseases known to have this effect on normal persons (fig. 6). Even in relatively mild infections with slight neutrophilic leukocytosis it was not uncommon to find a significant increase in the percentage of juvenile neutrophils (cf. fig. 6, case 4).

The leukocyte count was between 6,000 and 6,500 per cmm on the first day. However, about 90 per cent of the neutrophils were juvenile, with either rod-shaped or almost round nuclei. On the fourth day of treatment with antibiotics this ratio was reversed and the leukocyte count was about 3,700 per cmm.

Qualitative changes in the neutrophils, such as toxic granulation and pyknosis of the nuclei were occasionally seen in patients with the Pelger anomaly who suffered from severe infections. These changes as well as other changes in the neutrophils and the other leukocytes due to disease were found to be essentially the same in patients who had the Pelger anomaly as in other patients. Moreover, changes observed in the bone marrow were essentially the same in these two patient categories.

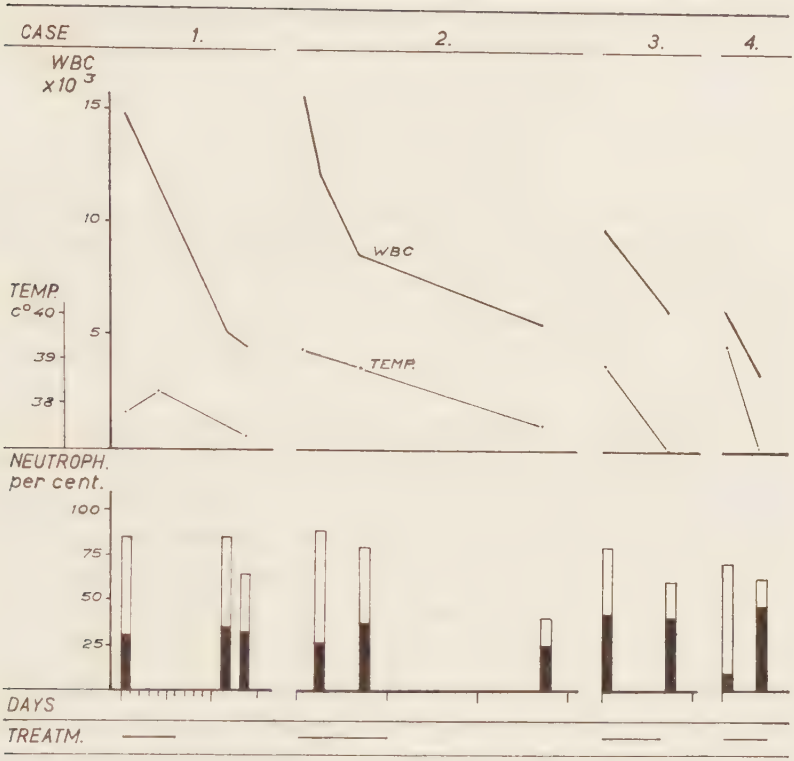

Fig. 6. The changes observed in the leukocyte counts, the percentage of neutrophils and the ratio between juvenile (unsegmented) and mature (segmented) neutrophils in four Pelger patients treated with antibiotics. The changes in the temperature are also shown. White area of column = unsegmented neutrophils, black area = segmented neutrophils.

Case 1: A 76 year old man (pedigree 8, III.3) with cardiac infarction and obstructive hyperplasia of the prostate.

Case 2: A 69 year old woman (pedigree 10, II.3) with cardiac sclerosis, auricular fibrillation and pulmonary embolism.

Case 3: A 10 year old boy (pedigree 20, IV.16) with scarlet fever and peritonsillar abscess.

Case 4: A 13 year old girl (pedigree 7, IV.3) with acute pharyngitis.

The patients, except Case 3, were treated daily with penicillin (400,000 I.E.) and streptomycinsulphate (0.50 g). Case 3 was treated with penicillin (600,000 I.E. daily).

FREQUENCY VARIATIONS OF THE PELGER ANOMALY

In the Department of Internal Medicine at Umeå Hospital differential leukocyte counts were routinely made in all patients admitted during the three year period from 1957 to 1959 inclusive. Later differential leukocyte counts were made less regularly, a fact confirmed by the hospital files from the first half of 1960.

During the three years from 1957 to 1959 in the Department of Internal Medicine 9,936 admissions of 7,235 patients were registered. Thus, 2,701 of the admissions were readmissions. A review of the available files over the three year period showed that differential leukocyte counts were made in 6,763 patients. It also showed that blood films had not been made from 146 patients probably due to accidental omissions. The hospital files of 326 patients were not available for study. It seems, however, reasonable to assume that these patients had been given the same routine blood tests as the other patients during the same period of time. Hence, during 1957 to 1959 inclusive a total number of 7,089 patients, *i. e.* 98 per cent of all first admissions, had differential leukocyte counts in the Department of Internal Medicine. Of this patient population 1.8 per cent (128) resided outside Västerbotten County and 2.9 per cent (212) in the northern coastal districts, while the remaining 95.3 per cent (6.749) lived in the southern coastal districts (cf. fig. 7 and table 15).

The frequency of the Pelger anomaly in the patients of the Department of Internal Medicine varied during the three year period from 1957 to 1959 as shown in table 11. The same frequency of the anomaly was found in 1957 and 1958 or 7.1

TABLE 11. *Frequency of the Pelger anomaly in the patient sample from the Department of Internal Medicine.*

Year of examination	Number of patients examined	Number of patients with the Pelger anomaly	Frequency of the Pelger anomaly per thousand
1957	2,802	20	7.1
1958	2,242	16	7.1
1959	2,045	8	3.9
1957—59	7,089	44	6.2

per thousand as compared with 3.9 per thousand in 1959. However, the variation in frequency between the different years is due to random variation. The average for the three year period was 6.2 per thousand. This frequency is much higher than any of those previously reported by other investigators.

In the Department of Otology and the Department of Infectious Diseases differential leukocyte counts were performed in the majority (on the average in more than 75 per cent) of patients admitted. Fully representative patient samples from these departments were, however, not obtained. Nevertheless the available data from 1957 to 1959 were corrected for readmissions of patients. Thereafter, the frequency of the anomaly in the patients of these departments was estimated. During the three years the frequency in the Department of Infectious Diseases was found to vary between 1.3 and 3.1 with a mean of 2.3 per thousand, and in the Department of Otology the frequency varied between 1.6 and 5.3 with a mean of 3.1 per thousand. The fact that differential leukocyte counts were not performed in all patients admitted during this period of time has been ignored in the calculation of the frequencies. Therefore the actual frequencies of the Pelger anomaly in the patients of these two departments must have been higher.

TABLE 12. *Comparison between the frequency of the Pelger anomaly found in patients in the present investigation and in previous investigations.*

Investigation	Type of patients	Total number	Pelger patients Total	‰
Nachtsheim (1960), Germany	Psychoneurotic and mentally deficient	2,508	1	0.4
Redies, Quenser, Tolksdorf, Saile & Wiedemann (1958), Germany	Same	4,772	4	0.8
Ebbing (1959 a), Germany	Hospital patients (unspecified)	4,373	1	0.2
The present investigation, Sweden	Hospital in-patients (Dept. of Int. Med.)	7,089	44	6.2

In table 12 the frequency of the Pelger anomaly in different groups of patients has been compared. The difference between the Swedish sample and the German ones is highly significant ($\chi^2 = 53{,}7$ 1 d. f., $P < 0.001$).

Assuming that the Pelger anomaly is not associated with a disease its frequency should be the same in a group of hospitalized patients as in a matched sample from the general population. The fact that the German investigators have found no significant difference between patients and normal healthy individuals (cf. tables 12 and 14) apparently supports this view. However, in the present investigation the frequency of the Pelger anomaly was significantly higher in the patient population than in all the groups of healthy individuals, such as blood donors, army recruits and schoolchildren added together (cf. table 13). Another high frequency was again found among the sample of schoolchildren (further discussion below).

TABLE 13. *The frequency of Pelger anomaly in the patients of the department of internal medicine (= patients sample) and in samples of healthy individuals.*

Individuals	Total number	Pelger individuals	
		Total	Per thousand
Blood donors, both sexes	1,614	4	2.5
Army recruits, age 20—22 years	1,598	4	2.5
Schoolchildren, age 13—14 years	308	2	6.5
Hospital in-patients (Dept. of Int. Med.)	7,089	44	6.2

Difference: Patients — Healthy individuals.
χ^2 5.3, 1 d.f., $0.02 < P < 0.05$.

TABLE 14. *Comparison between the frequency of the Pelger anomaly in German and Swedish schoolchildren.*

Investigation		Total number	Pelger-children	
			Total	‰
Wiedemann & Saile (1957)	Schoolchildren, age 6—19 years	15,097	3	0.8
Ebbing (1959 a)	Schoolboys, age 13—14 years	12,086	3	0.3
The present investigation	Schoolchildren, age 13—14 years	308	2	6.5

$\chi^2 = 22.4$, 1 d.f., $P < 0.001$.

The patient population was subdivided into parish samples, *i. e.* the patients of the Department of Internal Medicine were grouped by their places of residence (table 15). The parish

TABLE 15. *The distribution of the patients of the department of internal medicine (= the patients sample) by parishes (= parish samples) and regions.*

Region	Parish.	Number of individuals examined	Thereof Pelger Number	Per thousand
1.	Nysätra	170	—	
	Bygdeå	226	3	
	Sävar	228	5	
	Holmön	22	—	
		646	8	12.4
2.	Umeå, city	1264	10	
	Umeå, rural	985	6	
	Holmsund	423	4	
		2672	20	7.5
3.	Vännäs	439	4	
	Hörnefors	193	3	
	Nordmaling	317	1	
		949	8	8.4
4.	Degerfors	421	6	
	Örträsk	44	—	
	Bjurholm	222	—	
		687	6	8.7
5.	Lycksele	522	1	
	Fredrika	87	—	
	Åsele	168	—	
		777	1	1.3
6.	Sorsele	196	—	
	Stensele	224	—	
	Tärna	51	—	
	Vilhelmina	346	1	
	Dorotea	201	—	
		1018	1	1.0

7.	Skellefteå, town	44	—	
	Skellefteå, rural	32	—	
	Norsjö	28	—	
	Lövånger	17	—	
	Malå	13	—	
	Bureå	8	—	
	Jörn	8	—	
	Byske	7	—	
	Burträsk	55	—	
		212	0	0
	Living outside the county	128	—	—
	Total:	7089	44	6.2

Fig. 7. Division of Västerbotten County into regions (cf. table 15).

samples have since been grouped into seven regional samples, which correspond to a division of the Västerbotten County as shown in fig. 7, where they have been numbered from 1 to 7 (cf. table 15).

The frequency of the Pelger anomaly is remarkably high (around 1 per cent) in regions 1 to 4, *i. e.* in the parishes surrounding the City of Umeå (cf. fig. 2). In the parish of Sävar (shown in fig. 2 by the figure 22.4) five individuals with the Pelger anomaly were found among 228 examined (2.2 per cent).

In the regions 5 to 7, *i. e.* in the western and the northern parts of the county, the frequency was lower and approached the frequency reported in Germany by Nachtsheim (1950 a), *i. e.* 0.8 per thousand.

The difference in frequency of the anomaly between the regional samples 1—4 and 5—7 is significant ($\chi^2 = 11.6$, 1 d. f., $P < 0.001$).

In order to test the validity of the high frequency found in the southern coastal area a sample of schoolchildren from three different schools in regions 1 and 2 was examined (in Bygdeå and Holmsund Communities and Umeå Rural Community, cf. fig. 2 and table 15). The frequency of the Pelger anomaly (6.5 per thousand) in this sample agrees with the frequency in regions 1 and 2 as calculated from the patient material.

A significant difference in the frequency of the Pelger anomaly is noted between the schoolchildren in this study and the samples of schoolchildren studied in Germany (Ebbing 1959 a, Wiedemann & Saile 1957).

The frequency of the Pelger anomaly in the southern coastal area of the Västerbotten County is so far the highest on record.

The pronounced geographic variation in the frequency of the Pelger anomaly within this county explains the difference between the frequencies found in the patients and in healthy individuals. These results do not support the hypothesis of an

association between the Pelger anomaly and any particular disease or group of diseases since the patient sample and the samples of healthy individuals differ greatly with respect to their regional representation. Thus, the army recruits constitute a random sample of males from the whole county and also the blood donors originate from different parts of it. On the other hand, in the patient sample there is an overrepresentation of the population in regions 1 to 4, where the frequency of the Pelger anomaly is highest.

Genetic analysis

There were 97 probands available for the investigation of families (cf. Material and methods). However, the families of 14 of the probands could not be examined due to unwillingness on behalf of the probands and their relatives to participate in the investigation. Hence, for the examination of families 83 probands could be used.

In the families where the Pelger anomaly occurred a total of 521 individuals was examined, *i. e.* 311 individuals with the Pelger anomaly and 210 normal individuals. They were found to belong to 203 sibships in 41 different pedigrees of varying size.

The phenotype of both parents of 106 sibships was determined and without exception either the father or the mother was found to have the anomaly. Thus, families where neither the mother nor the father had the anomaly or families where both of them did have the anomaly were not observed.

The Pelger anomaly could repeatedly be traced through two or three and up to four generations without ever being found to "skip" a generation (fig. 8 and 9). Thus, according to the pedigrees the anomaly behaves strictly as a dominantly inherited trait.

By calculating the frequency of individuals with Pelger anomaly among the sibs of the 83 probands the following figures were obtained according to Weinberg's proband method (Weinberg 1925, Schulz 1936).

The figure obtained is in agreement with that expected for a dominant gene with full penetrance.

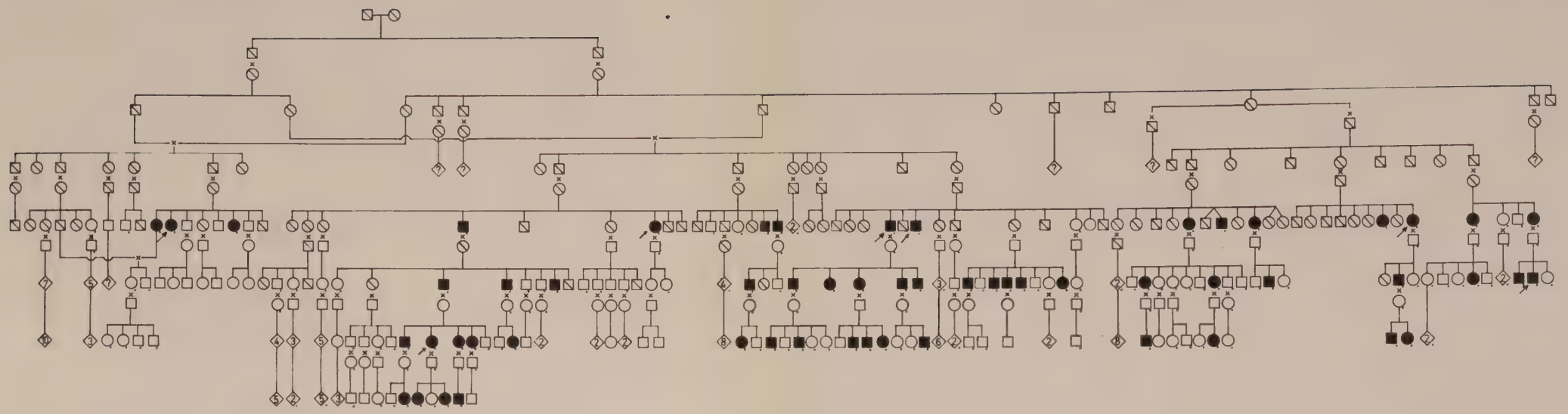

Fig. 8. Pedigree 1 (cf. Appendix).

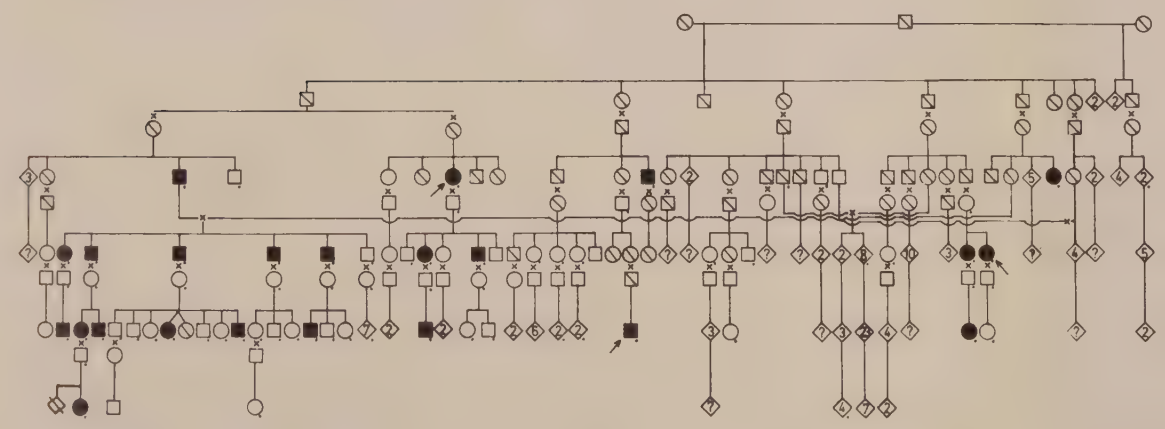

Fig. 9. Pedigree 2 (cf. Appendix).

= Female, unexamined.

= Male, unexamined.

= Examined, normal male and normal female.

= Examined, male and female with the Pelger anomaly.

= Proband.

= Parents.

= Dead (female).

= Sex and number of sibs unknown. A number within the diamond indicates the number of sibs in the sibship.

No. of sibships	73
Affected sibs of probands	85
No. of sibs of probands	152
Mendelian ratio	$85/152 = 0.56 \pm 0.06$

In 106 completely examined families (*i. e.* in which the phenotype of both parents was determined) the children who had the Pelger anomaly (129) were classified according to birth rank (cf. table 16). The close agreement between the total observed and expected figures shows that there is no association between the Pelger anomaly and birth order.

TABLE 16. *Birth rank of children with Pelger anomaly.*

Size of sibship	Number of Pelger children with rank									Expected no. each rank
	1	2	3	4	5	6	7	8	9	
1	(14)									—
2	18	14								16.00
3	16	15	7							12.67
4	3	2	6	4						3.75
5	4	4	5	7	1					4.20
6	4	4	3	2	3	3				3.17
7	—	—	—	—	—	—	—			—
8	—	—	—	1	—	—	—	1		0.25
9	—	1	—	—	—	—	1	—	—	0.22
Total obs.	45	40	21	14	4	3	1	1	—	129
Total exp.	40.3	40.3	24.3	11.6	7.8	3.6	0.5	0.5	0.2	129.1

The fitness of individuals heterozygous for the Pelger anomaly

Relative fitness or the selection value is usually defined as the fertility of one group of individuals relative to that of another. Thus, by the relative fitness of an individual possessing a certain gene is meant the extent to which that individual can

reproduce and contribute to the next generation. The reproductive fitness of persons having a certain trait is a measurement of their fertility relative to that of the general population or another representative group of normal individuals. Fitness can be deduced indirectly if the incidence of a particular trait and its mutation rate are known.

Pätau and Nachtsheim (1946) calculated the mutation frequency of the Pelger anomaly to be about 1×10^{-4} per gene per generation. On the basis of this result they estimated that persons with the Pelger anomaly should have a fitness that was about 20 per cent lower than that of normal individuals. Nachtsheim (1950 a) later pointed out that most probably the fitness of individuals with the Pelger anomaly deviated less from that of normal individuals. He presented (Nachtsheim 1954) new calculation of mutation rate, which he found to be about 2.7×10^{-5} per gene per generation, and estimated that individuals with the Pelger anomaly should have about 95 per cent of the fitness of normal persons.

Clarke (1959) counted the mean number of children of individuals with and without the Pelger anomaly, regardless of age or marital state, in a family previously examined (Davidson, Lawler and Ackerly 1954). He found that, on the average, persons with the anomaly had 1.0 and those unaffected 0.6 children. In the present investigation it was similarly found that individuals having the Pelger anomaly on the average had 1.4, their normal sibs 0.9, and their normal relatives 0.8 children. In terms of reproductive fitness this should mean that persons with the Pelger anomaly were considerably more fit (about 50 to 70 per cent) than their normal sibs and other relatives.

The estimation of fitness is always a difficult task as sources of bias may be concealed in the data or when bias is detectable be hard to correct for. The selection of a comparable normal

reference group is one of the major difficulties. In most cases only a small group of individuals with a certain trait is available for study, so that it is difficult to detect small differences in fitness.

In the present investigation an attempt to estimate the reproductive fitness of individuals with the Pelger anomaly was made by calculating the mean number of children of individuals with the Pelger anomaly and the children of their sibs in selected sibships. The sibships were selected so that at least one of the sibs had the Pelger anomaly and at least one of the other sibs was normal. The marital state and the age of individuals was ignored.

The results are shown in table 17, where also the distribution of sibs with their number of offspring is given. It was

TABLE 17. *Individuals with the Pelger anomaly and their normal sibs distributed by number of offspring.*

Number of offspring	Individuals with Pelger anomaly	Normal sibs of individuals with Pelger anomaly
0	103	95
1	20	21
2	32	16
3	22	16
4	9	7
5	7	3
6	6	—
7	—	3
8	1	2
9	—	—
10	1	—
Total:	201	163
Mean number of offspring:	1.37	1.11

found that the individuals with the Pelger anomaly on the average had 1.4 children, while their normal sibs had 1.1 children.

The fertility of individuals heterozygous for the Pelger anomaly is not significantly higher than that of normal persons ($0.2 > P > 0.1$). These results must be interpreted with great caution, but it seems justifiable at least to conclude that they do not indicate that the reproductive fitness of individuals heterozygous for the Pelger anomaly is decreased.

DISCUSSION

In this study the identification of the Pelger anomaly presented no difficulty. A rapid survey of blood films was usually sufficient for establishing the diagnosis. Atypical forms of the anomaly or the "partial form" ("Teilträger") were never met with. The typical dumb-bell shaped nuclei of the neutrophils together with absence of nuclei with more than two lobes make the blood picture of the Pelger anomaly clearly distinguishable from that of normal persons. The mean number of nuclear lobes was 1.4 in individuals heterozygous for the Pelger anomaly, but 2.8 in the normal individuals.

Distinctive changes in the nuclear chromatin of the Pelger neutrophils were constantly found. In no other condition are similar chromatin changes known, except in the "partial form" of the anomaly. Through this morphologic characteristic the Pelger anomaly can be differentiated from the blood picture that is found in diseases associated with an increase of unsegmented neutrophils. These chromatin changes also distinguish the true Pelger anomaly from the pathologic leukocyte changes that have been called the "acquired form" of the Pelger anomaly. In rare instances difficulties may be met with in classification. Thus, in individuals heterozygous for the Pelger anomaly, leukocyte changes similar to those described as typical for the homozygous state may be observed in association with disease (Lüers, Nachtsheim and Petzel, 1956).

In all the individuals with Pelger anomaly who were examined there was a great uniformity in the leukocyte characteristics. Familial or individual variations were not detected.

In the relatives of patients with gargoylism an increase in

the mean number of nuclear lobes of the neutrophils has been observed (Mittwoch, 1962). Undritz (1958) described a dominantly inherited condition that was characterized by hypersegmentation of the neutrophils. In the gargoylism, however, the deviation from the normal was slight. A decrease in the mean number of nuclear lobes in the neutrophils is found in mongolism (Shapiro, 1949, Mittwoch, 1958), but it is slight as compared with that of the Pelger anomaly. Thus the Pelger anomaly is clearly distinguishable from the other conditions showing genetically determined changes in nuclear segmentation.

In agreement with the results from previous investigations a low frequency of sex specific drumsticks was found in the neutrophils of females with the Pelger anomaly. In counting 500 neutrophils from females with the anomaly drumsticks were found in zero to four neutrophils, while in normal females they were found in six to eighteen (usually more than ten) neutrophils. This difference is of such a magnitude that it would allow a rather safe classification of the anomaly. The reduction in the number of drumsticks is, however, not specific for the Pelger anomaly, but is also found in mongolism (Mittwoch, 1958). On the other hand, in instances of nuclear hypersegmentation an increase in the number of cells with drumsticks is observed (Undritz 1960, Mittwoch, 1962). Thus, the number of cells containing nuclear drumsticks is directly related to the mean lobe count. Therefore, in the Pelger anomaly the reduction of the percentage of cells with drumsticks has no bearing on the nuclear sex.

A study of the chromosome number and karyotype of cultured leukocytes of the peripheral blood and bone marrow cells of individuals heterozygous for the Pelger anomaly showed no abnormalities. Most chromosomal aberrations thus far described in humans are associated with multiple gross changes in

the phenotype. It would seem most likely that if a chromosomal abnormality were responsible for the Pelger anomaly it is too small to be detected by currently used techniques.

Information on the mode of inheritance of the Pelger anomaly is mainly based on a number of case reports in the literature. In the population studied in the present investigation the frequency of the Pelger anomaly was unusually high, and therefore a large number of families was available for a genetic study. The results of this investigation show that the Pelger anomaly behaves as a dominant autosomal trait with full penetrance. No sporadic cases, i. e. cases where the offspring, but not the parents had the anomaly, were discovered. In the literature, however, sporadic cases of the anomaly have been reported (Zündel 1936, Stahel 1936, Jonsson, Boström & Bringel 1947, Jorde 1953, Scoler & Matter 1958, Skendzel & Hoffman 1962). The homozygous form of the Pelger anomaly was not observed nor was there a mating between individuals heterozygous for the anomaly. The presence of the heterozygous form of the Pelger anomaly in both parents has been reported in the literature only once (Havercamp Begemann and van Lookeren Campagne 1952).

Some of the probands were found to have common ancestors. Thus, in pedigree 1 seven "unrelated" probands were found to have a common ancestor that lived during the later half of the 18th century. Similarly a relationship between the probands in a number of other pedigrees could be traced to common ancestors (cf. Appendix).

In all the samples (patients, blood donors, army recruits and schoolchildren) drawn from the population of the investigation area the frequency of the Pelger anomaly is remarkably high as compared with that found in previous investigations. There are significant frequency variations within Västerbotten county. The highest frequency was found in the southern coa-

stal area, where on the average it was about 1 per cent. The population of this area is overrepresented in the patient sample, that shows a higher frequency of the anomaly than the samples of recruits and blood donors. The high frequency of the anomaly in the southern coastal area was further confirmed through a sample of schoolchildren. Consequently there is little reason to doubt that there are some remarkable local increases in the frequency of the Pelger anomaly in Västerbotten county. Of all possible explanations for this change of gene frequency, genetic drift seems to be the most likely one. The experience from the genealogic work in the present investigation strongly supports this assumption, for when tracing the relationship between different families the pedigrees were found to converge towards the areas where the frequency of the anomaly was highest (cf. Appendix). Thus, in some more or less isolated areas in the Västerbotten county local increases in the frequency of the Pelger anomaly may have taken place due to chance only. Böök (1953) and Kostmann & Böök (1956) have reported local increases in the frequency of schizophrenia and in the frequency of infantile genetic agranulocytosis in North Sweden, which most likely are to be interpreted as the result of genetic drift. Thus, the local variations in the frequency of the Pelger anomaly in Västerbotten County are with all probability also to be looked upon as an example of the peculiar gene frequency distribution that may arise in a population like that of North Sweden where more or less isolated population groups still can be found.

The frequency of the Pelger anomaly generally found (about 1 per thousand or less) in different populations is probably maintained by a balanced polymorphism. The results obtained from experiments on rabbits (Nachtsheim 1950 a) may suggest that in humans the homozygous form of the Pelger anomaly also is lethal or semilethal. This would cause a loss of Pelger

genes, which might be balanced by some advantage of the individuals heterozygous for the Pelger anomaly. I have made some attempts to compare the fitness of individuals having heterozygous Pelger anomaly with that of normal individuals. I have also tried to find whether any biological differences exist between the Pelger cells and normal blood cells.

In the mature Pelger neutrophils a normal alkaline phosphatase activity was found. This is in disagreement with the findings of Tempka, Hanicki and Uransinski (1961), who were unable to detect any alkaline phosphatase activity in Pelger neutrophils. In agreement with the results from previous investigations no abnormalities in the peroxidase activity of the Pelger leukocytes were detected.

Leitner and Gugelot (1938) reported a lower phagocytic activity of the Pelger neutrophils and assumed that individuals with the Pelger anomaly had a lessened resistence to infections. In this investigation the phagocytic activity of the Pelger leukocytes showed no obvious difference from that of normal leukocytes. Other investigators have come to the same conclusion (Terhorst 1957, Stobbe 1959 a).

The morphological characteristics found in the Pelger leukocytes resemble to some extent those of immature normal leukocytes. The immature cells seen in leukemia have been reported to have a lower rate of uptake of tritiated thymidine than normal cells (Alfrey, Kiely, Tauxe and Owen, 1961). There is, however, no obvious difference between the bone marrow cells from individuals with the Pelger anomaly and those of normal individuals in the *in vitro* rate of uptake of tritiated thymidine as measured by grain counts in autoradiograms. The fitness of individuals with the Pelger anomaly as compared to that of normal individuals has been discussed in some publications. The Pelger anomaly happened to be discovered first in persons suffering from tuberculosis (Pelger 1928). For some time there-

after the anomaly was suspected to have some causal association with that particular disease (Stahel 1936).

As late as 1952 Schilling discussed seriously the possibility that the Pelger anomaly was so strongly associated with nervous disorders that this might be of forensic importance ("geistige Minderwertigkeit"). I have personally examined a large number of individuals who have the Pelger anomaly without finding any accumulation of nervous disorders or other peculiarities. The individuals with Pelger anomaly found in the present investigation represented all social groups. When going through the literature on Pelger anomaly one is struck by the frequent occurrence of controversial statements and hasty conclusions, especially concerning the relation between the Pelger anomaly and disease.

In the present study the frequency of the Pelger anomaly is significantly higher in the patients than in the samples of normal individuals. This fact does not allow any conclusions to be drawn concerning an association between the Pelger anomaly and disease because the patients come mainly from the parts of the county where the frequency of the anomaly is high, while the normal individuals constitute a random sample of the whole population of the county. This illustrates an example of the kind of difficulties one may run into when selecting proper control groups.

The early speculation concerning association between the Pelger anomaly and disease were based on case reports or observations made in small groups of individuals with the anomaly (most often one or two families only). This sample of patients with the Pelger anomaly is the largest so far collected. However, it is too small to permit conclusions to be drawn concerning possible associations between the Pelger anomaly and diseases. Diseases listed in hospital records of the patients with the Pelger anomaly are given in the Appendix.

An attempt was made to calculate the fitness of individuals with the Pelger anomaly as compared with that of their normal sibs. In agreement with the results obtained by Clarke (1959) the individuals with the anomaly were found to have a somewhat higher number of children than their normal sibs, though this difference was not statistically significant.

SUMMARY

1. This investigation of the Pelger anomaly was based on the examination of blood films from about 15,000 patients of all the clinical divisions and out-patient services of Umeå Hospital, the Royal Medical School in Umeå, Sweden, during 1957—1960. Moreover, blood films from blood donors (1,614), army recruits (1,598) and schoolchildren (308) as well as a group of relatives of the probands discovered were examined. With few exceptions the individuals examined all resided in Västerbotten County. Upon examination of blood films 97 probands with the Pelger anomaly were discovered.

2. The Pelger characteristics were recognized without difficulty in the neutrophilic leukocytes. All the individuals (325) found to have the Pelger anomaly were apparently heterozygotes.

3. In the neutrophils showing the Pelger characteristics the average number of nuclear lobes was 1.4, whereas in normal neutrophils it was significantly higher, 2.8.

4. In the neutrophils from females with the Pelger anomaly the frequency of sex specific drumsticks was low, *i. e.* 0—4 per 500 neutrophils as compared to 6—18 (usually > 10) in the neutrophils from normal females.

5. Analysis of mitotic metaphase chromosomes of cultured bone marrow and peripheral blood cells from individuals with the Pelger anomaly showed an apparently normal karyotype.

6. The peroxidase activity and the alkaline phosphatase activity of the leukocytes with Pelger characteristics appeared to be within normal ranges. The phagocytic activity of these leukocytes was not significantly different from that of normal

leukocytes. The uptake of tritiated thymidine *in vitro* measured by grain counts in autoradiograms was about the same in bone marrow cells from individuals with the Pelger anomaly as in those from normal individuals.

7. In the hospital patients (88), who also had the Pelger anomaly, the pathologic changes of the leukocytes were essentially the same as in other patients afflicted with the same diseases.

8. The relatives of 83 probands were examined and found to belong to 41 pedigrees. In altogether 203 sibships 521 sibs were examined and the Pelger anomaly found in 228 of them (the probands excluded). A genetic analysis of the sibs of the probands confirmed that the Pelger anomaly is inherited as an autosomal dominant trait with full penetrance.

9. On the average, individuals with the Pelger anomaly had 1.4 children and their normal sibs 1.1 children. In terms of reproductive fitness this difference is not statistically significant.

10. All samples drawn from the population of Västerbotten County displayed a high frequency of individuals with the Pelger anomaly:

Type of sample	Frequency per thousand	Number of examined individuals
Hospital patients	6.2	7.089
Blood donors	2.5	1,614
Army recruits	2.5	1,598
Schoolchildren	6.5	308

The frequency figures previously reported have all been less than 1.0 per thousand.

Significant regional variations in the frequency of the Pelger anomaly occurred in the population of the investigation area. In the parishes of the southern coastal area the highest frequencies (up to about 2 per cent) were found. Some of these local differences may be due to genetic drift.

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APPENDIX

Summary of primary family data

Explanation of symbols:

M = male; F = female; P = individual with the Pelger anomaly; N = normal individual; D = dead, but information on year of death lacking; a = first marriage; b = second marriage.
Absence of symbols in columns 4, 6 and 7 indicate that data are lacking.

Diagnoses have been listed with code numbers according to the International Classification of Diseases (WHO 1957).

1. Primary data on pedigrees.

Pedigree 1.

Parents		Offspring					
Number in pedigree	Phenotype ♂×♀	Number in pedigree	Year of Birth	Year of Death	Sex	Phenotype	Comments
1	2	3	4	5	6	7	8
		I:1	1757	1835	M		
		2	1749	1835	F		
I:1,2		II:1	1785	1857	M		
		2	1793	D	M		
II:1		III:1	1812	1888	M		Married to III:3.
		2	1820	1891	F		Married to III:6.

1	2	3	4	5	6	7	8
II:2		III:3	1817	1900	F		Married to III:1.
		4	1819	D	M		
		5	1820	D	M		
		6	1823	1900	M		Married to III:2.
		7	1825	1827	F		
		8	1826	D	M		
		9	1827	1830	M		
		10	1830	1895	F		
		11	1832	D	M		
		12	1837	D	M		
III:1,3		IV:1	1841	1917	M		
		2	1843	D	F		
		3	1848	1931	M		
		4	1852	1908	F		
		5	1855	1888	F		
		6	1859	1942	M		
		7	1862	D	F		
III:2,6		IV:8	1844	1845	F		
		9	1846	1912	M		
		10	1848	1926	M		
		11	1850	1899	F		
		12	1853	1856	F		
		13	1855	1886	F		
		14	1858	1924	M		
		15	1861	1921	F		
III:10		IV:16	1858	1870	M		
		17	1860	1917	M		
		18	1862	1862	F		
		19	1863	1864	M		
		20	1865	D	F		
		21	1867	1895	M		
		22	1870	1870	M		
		23	1872	1873	F		
		24	1873	1948	M		
IV:1		V:1	1876	1943	M		
IV:3		V:2	1884	1919	F		
		3	1889	1959	F	N	
		4	1891	1941	M		Married to V:10.
		5	1893	1893	F		
		6	1895		F	N	

1	2	3	4	5	6	7	8
IV:4		V:7	1894		M		
IV:5		V:8	1886		M	N	
		9		D	M		
IV:6		V:10	1902		F	P	Married to V:4.
		11	1904		F	P	Proband. Chronic nephritis (592).
		12	1905		M		
		13	1908	1956	F		
		14	1910		M		
		15	1914		F	P	
		16	1916		M		
		17	1921	1922	M		
IV:9		V:18	1873	1958	F		
		19	1875	1935	F		
		20	1876	D	F		
		21	1878		M	P	
		22	1879	1880	M		
		23	1880	1928	F		
		24	1883		F	P	Proband. Cholelithiasis (584).
		25	1886	1887	M		
		26	1887	1887	M		
IV:10		V:27	1879	1935	M		
		28	1882		M	N	
		29	1885	1953	M		
		30	1887		F	N	
		31	1890	1950	F		
		32	1894		M	P	
		33	1897		M	P	
IV:11		V:34	1887		M	N	
		35	1890		M	N	
IV:13		V:36	1883	1889	F		
		37	1886	1887	F		
IV:15		V:38	1881	1904	M		
		39	1882	1930	F		
		40	1884	1891	F		
		41	1886	1958	M	P	Proband. Pyelonephritis (600.0).
		42	1888	1888	M		

1	2	3	4	5	6	7	8
		43	1890	1958	M	P	Proband. Essential malignant hypertensive heart disease (441).
		44	1892	1957	F		
		45	1894	D	M		
		46	1896	1956	F		
		47	1898	1918	M		
		48	1900		F	N	
		49			F		Emigr. to N. Amer.
		50	1904	1919	M		
IV:17		V:51	1893	D	F		
		52	1894	1896	F		
		53	1895	1916	M		
		54	1897	1917	F		
		55	1899		F	P	
		56	1902	1920	M		
		57	1902		M	P	
		58	1904	1920	F		
		59	1908		F	P	
		60	1910	1919	F		
		61	1910	1918	F		
IV:20		V:62	1891	1918	M		
		63	1892	1923	F		
		64	1894	1894	M		
		65	1895	1922	M		
		66	1897	1901	F		
		67	1900	1901	F		
		68	1902		F	P	
		69	1904	1917	F		
		70	1905		F	P	Proband. Varicose veins of lower extremities (460).
IV:24		V:71	1911		F	P	
		72	1915		F	N	
		73	1917		M	N	
		74	1919		F	P	
V:3	x N	VI:1	1911	1931	F		
		2	1913		F	N	
		3	1917		M	N	

1	2	3	4	5	6	7	8
		4	1921		F		
		5	1923		M	N	
		6	1925		F	N	
		7	1928		M		
V:6	N x N	VI:8	1921		F		
		9	1924		M	N	
		10	1926		M		
		11	1929		M		
		12	1934		M		
V:4,10	x P	VI:13	1928		F	N	
		14	1932		M	N	
V:12		VI:15	1935		M		
		16	1942		F		
		17	1945		M		
V:13		VI:18	1937		F		
		19	1940		M		
V:16		VI:20			F		
		21			F		
V:19		VI:22	1899	1899	F		
		23	1900		M	N	
		24	1904		F	N	
		25	1917	1917	M		
V:20		VI:26	1910		F	N	
V:21	P x	VI:27	1901		F	N	
		28	1903	1936	F		
		29	1905		M	P	
		30	1907		M	P	
		31	1909		M	N	
		32	1911		M	N	
		33	1914		M	P	
		34	1917	1917	M		
V:23		VI:35			M	N	
		36	1907		M	N	
		37	1909		M		
		38	1911		M	N	
		39	1914	1920	M		
V:24	N x P	VI:40	1919		F		
		41	1922		F	N	
V:29		VI:42	1907		M	N	
		43	1911		M	N	

1	2	3	4	5	6	7	8
		44	1913		F	N	
		45	1922		M	N	
V:33	P x N	VI:46	1926		M	P	
		47	1936	1937	F		
		48	1938		M	N	
V:41	P x N	VI:49	1917		M	P	
		50	1921		F	P	
		51	1922		F	P	
		52	1924		M	P	
		53	1925		M	P	
V:44		VI:54	1910		F	N	
		55	1912		F	N	
		56	1914		M	N	
V:45	x N	VI:57	1926		M	N	
V:46		VI:58	1923		M	P	
		59	1925		M	N	
		60	1927		M	P	
		61	1928		M	P	
		62	1930		M	P	
V:46		VI:63	1932		M	N	
		64	1936		F		
		65	1939		F	P	
V:48	x N	VI:66	1928		F	N	
V:51		VI:67	1919		M	N	
		68	1922		F	N	
V:55	N x P	VI:69	1922		M	N	
		70	1924		F	P	
		71	1925		F	N	
		72	1927		F	N	
		73	1929		F	N	
		74	1930		M	N	
		75	1932		F	P	
		76	1934		M	N	
		77	1938		M	N	
V:59	N x P	VI:78	1932		M	N	
		79	1937		M	P	
		80	1941		F	N	
V:70	N x P	VI:81		D	F		
		82	1932		M	P	
		83	1941		F	N	

1	2	3	4	5	6	7	8
V:71	N x P	VI:84	1934		F	N	
		85	1935		M	N	
		86	1936		F	N	
		87	1941		F	P	
		88	1952		M	N	
V:72	N x N	VI:89	1943		M	N	
		90	1947		M	N	
V:74	N x P	VI:91	1946		M	P	
		92	1948		M	P	Proband. Observation, without need for further medical care (793).
		93	1955		F	N	
VI:2	x N	VII:1	1946	1946	F		
		2	1948		M		
VI:3	N x N	VII:3	1954		M	N	
		4	1958		M	N	
VI:4		VII:5	1949		F		
		6	1953		M		
VI:5	N x	VII:7			M	N	
VI:6	x N	VII:8	1946		F		
		9	1952		F	N	
		10	1958		M	N	
VI:8		VII:11	1947		F		
		12	1956		M		
VI:9	N x	VII:13	1944		M		
VI:13	N x N	VII:14	1947		F	N	
		15	1949		F	N	
		16	1953		M	N	
		17	1955		M	N	
VI:23	N x N	VII:18	1926		M	N	
		19	1927		F		
		20	1931		M		
		21	1947		F	N	
VI:24	x N	VII:22			F	N	
		23			M	N	
		24			F		
VI:26	x N	VII:25	1931		F	N	
		26	1934		F	N	
		27	1939		M		

1	2	3	4	5	6	7	8
		28	1946		F	N	
		29	1951		M	N	
VI:27	x N	VII:30	1921		F		
VI:28		VII:31	1927		M	N	
		32	1928		M		
		33	1930		F	N	
		34	1934		M	N	
VI:29	P x N	VII:35	1928		M	P	
		36	1930		F	P	Proband. Bronchopneumonia (491).
		37	1931		F	P	
		38	1937		F	P	
		39	1941		M	N	
VI:30	P x N	VII:40	1936		M	N	
		41	1941		F	P	
VI:31	N x N	VII:42	1935		M		
VI:32	N x N	VII:43	1944		F		
		44	1948		M	N	
VI:36	N x	VII:45	1937		F		
		46	1941		F		
VI:37		VII:47	1937		F		
VI:38	N x	VII:48	1935		M		
		49	1947		M		
VI:40		VII:50			M		
		51			M		
VI:42	N x	VII:52	1933		M		
		53	1935		F		
		54	1937		M	N	
		55	1945		F	N	
		56	1946		F		
VI:43	N x N	VII:57	1937		M		
		58	1941		M	N	
VI:45	N x N	VII:59	1948		M	N	
VI:46	P x N	VII:60	1948		F	P	
		61	1951		M	N	
VI:49	P x N	VII:62	1943		M	P	
		63	1944		M	N	
		64	1947		M	P	

1	2	3	4	5	6	7	8
		65	1950		F	N	
		66	1951		F	N	
VI:51	x P	VII:67	1940		M		
		68	1943		M	P	
		69	1948		M	P	
		70	1954		F	P	
VI:52	P x N	VII:71	1948		F	N	
		72	1952		F	N	
		73	1956		M	P	
VI:54	x N	VII:74			F		
		75			M	N	
		76			F	N	
		77			M		
VI:55	x N	VII:78			F		
		79			F		
VI:57	N x N	VII:80	1953		M	N	
		81	1957		M	N	
VI:58	P x	VII:82	1951		M	N	
		83	1953		M	N	
VI:61	P x	VII:84	1958		M		
VI:64		VII:85					
		86					
VI:66	N x N	VII:87	1958		M	N	
VI:67	N x	VII:88	1943		F		
		89	1944		M		
		90	1949		F		
		91	1954		F		
VI:68	N x N	VII:92	1941		F	N	
		93	1948		M	N	
		94	1949		F	N	
		95	1952		F	N	
VI:70	N x P	VII:96	1952		M	P	
VI:71	x N	VII:97	1956		F		
VI:72	N x N	VII:98	1952		F	N	
		99	1955		M	N	
VI:75	x P	VII:100	1954		F	N	
		101	1958		F	P	
VI:76	N x N	VII:102	1957		F	N	
VI:82	P x N	VII:103	1954		M	P	
		104	1958		F	P	

1	2	3	4	5	6	7	8
VI:84	x N	VII:105	1957		M	N	
		106	1959		M	N	
VII:18	N x	VIII:1	1957		M		
		2	1959		M		
VII:19		VIII:3			F		
		4			F		
VII:20		VIII:5			M		
VII:22	N x N	VIII:6	1950		M	N	
		7	1953		F	N	
VII:25a	x N	VIII:8	1952		M	N	
VII:25b	x N	VIII:9	1957		M	N	
VII:26	N x N	VIII:10	1954		F	N	
		11	1956		F	N	
		12	1958		M	N	
VII:30		VIII:13			F		
		14			F		
		15			M		
VII:31	N x N	VIII:16	1957		M	N	
VII:32		VIII:17			M		
VII:33	x N	VIII:18	1953		F	N	
VII:35	P x N	VIII:19	1957		M	N	
		20	1959		F	P	
VII:36	N x P	VIII:21	1951		F	P	
		22	1955		F	N	
		23	1958		F	P	
VII:37	N x P	VIII:24	1959		M	P	
VII:38	N x P	VIII:25	1959		M		

Pedigree 2.

1	2	3	4	5	6	7	8
		I:1	1812	D	F		
		2	1810	D	M		
		3	1845	1901	F		
I:1,2		II:1	1836	1922	M		
		2	1837	1913	F		
		3	1838	D	M		Emigr. to N.Amer.

1	2	3	4	5	6	7	8
		4	1840	D	F		
		5	1841	D	M		
		6	1842	1903	M		
		7	1843	D	F		
		8	1844	D	F		
		9	1846	D	M		
		10	1852	1854	M		
I:2,3		II:11		D	M		Emigr. to N.Amer.
		12		D	F		Emigr. to N.Amer.
		13	1875	1931	M		
II:1a		III:1	1866	1897	M		
		2	1869	1887	F		
		3	1870	D	M		Emigr. to N.Amer.
		4	1873	1959	F		
		5	1874		M	P	Married to III:30.
		6	1879		M	N	
II:1b		III:7	1891		F		
		8	1893	1910	F		
		9	1894		F	P	Proband. Diabetes mellitus (260).
		10	1895	D	M		
		11	1896	1902	F		
II:2		III:12	1874	1923	M		
		13		1904	F		
		14	1877		M	P	
II:4		III:15	1861	D	F		
		16	1863	D	F		
		17	1865	1958	F		
		18	1866	D	F		
		19	1871	D	M		
II:4		III:20	1873	1959	M	N	Married to III:26.
		21	1883	D	M		
		22	1885		M	N	
		23	1886		M		Married to III:37.
II:5		III:24	1872	D	M		
		25	1873	D	M		
		26		1957	F		Married to III:20.
		27		D	F		
		28		D	M		

1	2	3	4	5	6	7	8
II:6		III:29	1874	D	M		
		30	1876	1934	F		Married to III:5.
		31	1878	D	F		
		32	1883	1894	M		
		33	1885		F		Emigr. to N.Amer.
		34	1888		F		Emigr. to N.Amer.
		35	1890	D	F		Emigr. to N.Amer.
		36	1892		F	P	
II:8		III:37	1878	D	F		Married to III:23.
		38	1879		M		Emigr. to N.Amer.
		39	1879		M		Emigr. to N.Amer.
II:13		III:40	1902	D	M		
		41	1904		M	N	
		42	1905	D	F		
		43	1908	D	M		
		44	1912		M	N	
		45	1915	D	F		
III:4		IV:1			F		
III:5,30	P x	IV:2	1898		F	P	
		3	1901		M	P	
		4	1904		M	P	
		5	1907		M	P	
		6	1912		M	P	
		7	1917		M	N	
III:7		IV:8			F		
III:9		IV:9	1917		M	N	
		10	1919		F	P	
		11	1923		F		
		12	1929		M	P	
		13	1934		M		
III:12		IV:14	1913	1946	M		
		15	1915		F	N	
		16	1917		F	N	
		17	1920		F	N	
		18	1928		M		
III:13	N x	IV:19		D	F		
		20	1902	D	F		
III:14	P x	IV:21	1922	1933	F		
III:18		IV:22	1890	1960	F	N	

1	2	3	4	5	6	7	8
		23	1900	1958	F		
		24	1904		M	N	
III:22	N x	IV:25			F		
		26			M		
III:20,26	N x	IV:27			M	N	
		28		D	F		
		29			F	N	
		30			M	N	
		31			F	N	
		32			M	N	
		33			M	N	
		34			F	N	
		35			F		
		36	1921		M	N	
III:24		IV:37	1898		F	N	
III:25		IV:38	1901	D	M		
		39			M		
		40			M		
		41			F		
		42		D	F		
		43			F	N	
		44			M		
		45			F		
		46			F		
		47	1921		M		
III:27		IV:48			F		Emigr. to N.Amer.
		49			F		Emigr. to N.Amer.
		50			F		Emigr. to N.Amer.
III:28	x N	IV:51	1916		F	P	
		52	1920		F	P	Proband. Observation, without need for further medical care (793).
III:23,37		IV:53			M		
		54			F		
		55			F		
		56			M		
III:41	N x	IV:57			F		
		58			F		
III:44	N x N	IV:59	1942		M		

1	2	3	4	5	6	7	8
		60	1945		F	N	
		61	1949		M	N	
IV:1		V:1			F		
IV:2	N x P	V:2	1922		M	P	
IV:3	P x N	V:3	1931		F	P	
		4	1934		M	P	
IV:4	P x N	V:5	1936		M	N	
		6	1940		M	N	
		7	1941		F	N	
		8	1944		F	P	
		9	1944	1945	F		
		10	1950		M	N	
		11	1952		F	N	
		12	1954		M	P	
IV:5	P x N	V:13	1934		F	N	
		14	1935		M	N	
		15	1941		F	N	
IV:6	P x N	V:16	1948		M	P	
		17	1954		M	N	
		18	1957		F	N	
IV:7	N x N	V:19	1939		M	N	
		20	1943		F	N	
		21	1945		M	N	
		22	1950		F	N	
		23	1951		M	N	
		24	1955		F	N	
		25	1957		F	N	
IV:8		V:26			F		
		27			F		
IV:10	N x P	V:28	1949		M	P	
IV:11		V:29			F		
		30			F		
IV:12	P x N	V:31	1953		F	N	
		32	1956		M	N	
IV:14		V:33			F		
		34			F		
IV:15	x N	V:35			F		
		36		D	F		
		37	1939		F	N	
		38	1942		F	N	

1	2	3	4	5	6	7	8
		39	1942		M	N	
		40	1947		M	N	
IV:16	x N	V:41	1945		F	N	
		42	1950		M	N	
IV:17	x N	V:43			M	N	
		44			F	N	
IV:20		V:45	1934		M	P	Proband. Pyrexia of unknown origin (788.8). Debility and undue fatigue (790.1). Schizoid personality (320.0). Later examined as blood donor.
IV:22	x N	V:46	1909		M		
		47	1912		F	N	
		48	1915	1950	F		
IV:23		V:49	1923		F	N	
IV:27	N x N	V:50			F		
		51			M		
		52			M	N	
IV:28		V:53			F	N	
		54			M		
		55			M		
IV:29	x N	V:56			F		
IV:30	N x N	V:57			M		
		58			M	N	
		59			M	N	
IV:31	N x N	V:60			M		
		61			M		
		62			M	N	
		63			F		
		64			F	N	
IV:32	N x N	V:65			F		
IV:33	N x N	V:66			M	N	
		67	1941		M	N	
		68			M	N	
		69			M	N	
		70			F	N	

1	2	3	4	5	6	7	8
IV:34	N x N	V:71			M		
IV:36	N x N	V:72			F		
		73			F	N	
		74			M	N	
		75			M	N	
IV:37	x N	V:76	1922		M		
		77	1925		M		
		78	1926		M		
		79			M		
IV:51	N x P	V:80	1942		F	P	
IV:52	N x P	V:81	1946		F	N	
IV:58		V:82			F		
		83			F		
V:3	N x P	VI:1	1956	1956			
		2	1960		F	P	
V:5	N x	VI:3	1961		M		
V:13	x N	VI:4	1956		F	N	
V:50		VI:5			M		
V:54	x N	VI:6			F	N	
		7			F	N	
		8			M	N	
V.56		VI:9			M	N	
		10					
		11					
V:65		VI:12			F		
		13			F		
		14			F		
V:71		VI:15					
V:76		VI:16			F		
		17			F		

Pedigree 3.

1	2	3	4	5	6	7	8
		I:1	1822	D	M		
		2	1823	D	F		

1	2	3	4	5	6	7	8
I:1,2		II:1	1848	1856	F		
		2	1849	1906	F		
		3	1851	1856	F		
		4	1853	1856	M		
		5	1855	1856	F		
		6	1858	1937	M		
		7	1861	1889	M		
		8	1863	1915	F		
		9	1866	1917	M		
		10	1869	1909	F		
II:2		III:1	1871	1934	F		
		2	1872	1919	M		
		3	1873	1873	M		
		4	1874	1914	M		
		5	1876	1951	M		
		6	1878	1949	M		
		7	1880	1939	M		
		8	1883	1936	M		
		9	1885		M	P	
		10	1892	1930	F		
II:6a		III:11	1887	D	M		Emigr. to N.Amer.
II:6b		III:12	1891	1891	M		
II:8		III:13	1890		M	P	
		14	1891	1918	M		
		15	1894		M	P	
		16	1895		F	N	
		17	1897		M	P	
		18	1899		M		
II:9		III:19	1895		M	P	
		20	1897		M	N	
		21	1898	1934	M		Emigr. to N.Amer.
		22	1901	1916	F		
		23	1902	1904	M		
		24	1905		F		
		25	1908		M	N	
		26	1910		F		
		27	1912		M		
		28	1914		M	P	
III:2		IV:1	1898		M	N	

1	2	3	4	5	6	7	8
		2	1899		M	P	Proband. Cirrhosis of liver (581). Varicose veins of oesophagus (462.1).
		3	1901		F	P	Proband. Irritability of colon (573.2).
		4	1903		F	P	
		5	1905	1940	M		
		6	1907	1915	M		
		7	1910	1915	M		
		8	1912		M		
		9	1914		F		
		10	1917		M	N	
III:4a		IV:11	1905		F		
III:4b	x N	IV:12	1909		M	N	
		13	1911		F		
		14	1913		F		
III:6		IV:15	1909		M	N	
		16	1912		F	P	
		17	1916		M	N	
III:7	x N	IV:18	1921		M	N	
		19	1923		M	N	
III:8		IV:20	1910	1911	M		
		21	1911	1927	M		
		22	1913		M	N	
		23	1914		M	N	
		24	1918		M	N	
		25	1920		F		
		26	1927	1929	M		
III:13	P x	IV:27	1921	1936	M		
III:16	N x N	IV:28	1921		M	N	
		29	1926		F	N	
		30	1935		M		
III:17	P x N	IV:31	1923		M	N	
		32	1928		F		
		33	1930		M	N	
III:18		IV:34					

1	2	3	4	5	6	7	8
III:19		IV:35	1920		M	N	
		36	1930		M	P	Proband. Peritonsillar abscess (511).
		37	1938		M		
III:20	N x N	IV:38	1923		M		
		39	1927		M		
		40	1929		M		
		41	1931		F	N	
		42	1944		F	N	
III:24		IV:43	1933		F		
		44	1934		M		
		45	1936		M		
		46	1946		M		
III:25	N x N	IV:47	1936		M	N	
		48	1941		F		
		49	1941		F		
III:26		IV:50	1949		F		
III:27		IV:51	1944		F		
		52	1953		M		
III:28		IV:53	1942		M	P	
		54	1950		F	N	
IV:4	N x P	V:1	1922		M	N	
		2	1925		M	P	
		3	1928		F	P	
IV:8		V:4			M		
		5			F		
IV:9		V:6	1939	1947	F		
IV:10	N x N	V:7	1952		M	N	
		8	1956		M	N	
IV:11		V:9	1928		M		
		10	1931		F	N	
		11	1938		M		
IV:12	N x	V:12	1933		F		
		13	1942		F		
IV:13		V:14			M		
IV:14		V:15					
		16					
IV:15	N x N	V:17	1935		M	N	

1	2	3	4	5	6	7	8
		18	1937		M	N	
		19	1939		F	N	
IV:16	N x P	V:20	1944	1959	F	P	Proband. Malignant neoplasm of sinus ethmoidal (160).
		21	1954		F	N	
IV:17	N x N	V:22	1944		M	N	
		23	1948		M	N	
		24	1952		M	N	
IV:9,22	N x	V:25	1949		F		
IV:22	N x	V:26	1937		F		
		27	1939		M		
IV:23	N x N	V:28	1937		F		
		29	1942		M		
		30	1943		F		
IV:28	N x N	V:31	1949		F	N	
		32	1953		M	N	
IV:31	N x N	V:33	1953		M	N	
		34	1956		F	N	
IV:32		V:35	1948		M	N	
IV:33	N x N	V:36	1953		M	N	
		37	1956		F	N	
IV:35	N x	V:38	1951		F	N	
		39	1957		F		
IV:36	P x N	V:40	1953		M	N	
IV:43		V:41	1957		F		
V:1	N x N	VI:1	1949		M	N	
		2	1952		F	N	
		3	1957		M	N	
V:3	N x P	VI:4	1950		F	P	
		5	1952		M	N	
V:9		VI:6	1954		F		
		7	1958		F		
V:10	x N	VI:8	1952		M		
		9	1956		M		
		10	1957		M		
		11	1959		M		

Pedigree 4.

1	2	3	4	5	6	7	8
		I:1	1853	1928	M		
		2	1860	1915	F		
I:1,2		II:1	1880	1955	F		
		2	1882	D	M		
		3	1885	1904	F		
		4	1887	1958	M	P	Proband. Arteriosclerotic heart disease (420).
		5	1890	1955	F		
		6	1892		F	N	
		7	1895	1927	F		
		8	1898		M	N	
		9	1901		M	P	Proband. "Paraparesis spastica" (357).
		10	1904	1904	F		
II:1		III:1	1913		F	P	Proband. Malignant neoplasma of mammary gland (170).
		2	1914		F	P	
		3	1916		M	P	
		4	1922		M	N	
		5	1924		F	P	
II:2		III:6	1912		F	N	
		7	1914		M	N	
		8			M	N	
II:6	N x N	III:9	1915		M	N	
		10	1922		F	N	
		11			M		
		12	1925		F	N	
II:8	N x N	III:13			M	N	
		14			M	N	
		15			M	N	
		16			M	N	
		17			F	N	
		18			F	N	
		19			F	N	
		20			M	N	

1	2	3	4	5	6	7	8
III:1	N x P	IV:1	1939		F	P	
		2	1941		M	N	
		3	1943		M	N	
		4	1945		F	N	
		5	1947		M	P	
		6	1955		M	N	
III:2		IV:7	1935		F	N	
		8	1937		M	P	
		9	1939		F	P	
		10	1943		M	N	
		11	1950		F	P	
		12	1956		F	P	
III:3	P x N	IV:13	1952		M	P	
		14	1956		F	P	
III:4	N x N	IV:15	1949		F	N	
		16	1951		M	N	
III:5	N x P	IV:17	1947		F	N	
		18	1951		M	N	
		19	1959		F	N	
III:6	x N	IV:20	1938		M		
		21	1943		F	N	
		22	1945		M	N	
		23	1947		M	N	
		24	1950		F	N	
III:7	N x N	IV:25			F	N	
		26			F	N	
III:8	N x N	IV:27			M		
		28			M		
III:9	N x N	IV:29			F	N	
		30			F	N	
		31	1958		M	N	
III:11		IV:32					
III:14	N x	IV:33	1958		M		
IV:7	N x N	V:1	1959		F		
IV:25	N x N	V:2	1956		M	N	

Pedigree 5.

1	2	3	4	5	6	7	8
		I:1	1803	1872	M		
		2	1805	1889	F		
I:1,2		II:1	1831	1900	M		
		2	1837	1921	M		
		3	1840	1905	F		
		4	1844	1915	F		
		5	1847	1925	M		
		6	1849	D	F		
II:3		III:1	1871	1945	M		
II:4a		III:2	1880		M	P	
II:4b		III:3	1886	D	M		
		4	1891	1955	F		
III:1a		IV:1	1896		F	P	
III:1b		IV:2	1913		F		
		3	1916		M	P	
		4	1918		F	N	
III:2	P x	IV:5	1907		F	N	
		6	1909		M	N	
		7	1910		M	N	
		8	1912		F	P	
		9	1914		F	N	
III:3		IV:10	1915		M		
		11	1920		M	P	
		12	1923		M	P	
III:4	N x	IV:13	1923		M	P	Proband. Backache NOS (787.5). Oligophrenia (325.5).
		14	1926		F	N	
IV:1	x P	V:1	1915		M	P	
		2	1918		F	P	
		3	1930		F	N	
		4	1930		M	P	
IV:2		V:5	1930		F	N	
		6	1932		F	N	
IV:3	P x N	V:7	1948		M	N	
IV:4	x N	V:8	1945		F		
		9	1957		M	N	
IV:6	N x	V:10			F		

1	2	3	4	5	6	7	8
IV:7	N x N	V:11	1946		F	N	
		12	1948		F	N	
		13	1950		F	N	
		14	1952		M	N	
IV:8	N x P	V:15	1942		M	P	
		16	1945		M	P	
		17	1947		F	N	
IV:9	x N	V:18	1945		F	N	
		19	1947		M		
IV:10		V:20			M		
		21			F		
IV:14	N x N	V:22	1946		F	N	
		23	1948		M	N	
		24	1951		F	N	
		25	1953		M		
		26	1959		M	N	
V:1	P x N	VI:1	1946		M	P	
V:2	N x P	VI:2	1945		F	P	
		3	1951		F	P	Proband. Hypertrophy of tonsils and adenoids (510.1).
		4	1958		M	N	
V:3	N x N	VI:5	1953		M	N	
		6	1958		M	N	
		7	1959		F		
V:4	P x N	VI:8	1956		F	P	
V:5	x N	VI:9	1949		F		
		10	1951		M		
		11	1955		M		
V:6	N x N	VI:12	1957		F	N	
		13	1959		F	N	
		14	1959		F	N	

Pedigree 6.

1	2	3	4	5	6	7	8
		I:1	1858	1920	M		
		2	1866	1939	F		

1	2	3	4	5	6	7	8
I:1,2		II:1	1889	D	F		
		2	1892	1957	M	P	Proband. Pneumonia (490).
		3	1895	1935	F		
		4	1898	1939	M		
		5	1901		M	P	
		6	1904		F	N	
		7	1909		F		
II:1		III:1			F		
II:2	P x N	III:2	1918		F	P	
		3	1919		F	N	
		4	1921		M	N	
		5	1931		M	P	
II:4		III:6	1921		M	P	
		7	1922		F	N	
		8	1926		M	N	
		9			F		
		10		D	F		
		11	1931		F	N	
		12	1933		M	N	
		13	1934		F	N	
II:5	P x N	III:14	1931		F	P	
		15	1934		M	P	Proband. Blood donor.
		16	1943		F	N	
II:6	x N	III:17	1933		F	N	
		18	1936		F	N	
		19	1946		F	N	
II:7		III:20			M		
		21			M		
III:2	N x P	IV:1	1941		M	P	
III:3	x N	IV:2	1938		F	N	
		3	1941		F	N	
		4	1946		M	N	
		5	1955		M	N	
III:4	N x	IV:6	1946		M	N	
		7	1949		F	N	
		8	1950		M	N	

1	2	3	4	5	6	7	8
III:5	P x N	IV:9	1955		F	P	
		10	1958		F	P	
		11	1959		M	N	
III:6	P x N	IV:12	1948		M	N	
III:7	x N	IV:13			F	N	
III:9		IV:14			F		
		15			F		
III:12	N x N	IV:16	1959		F	N	
III:14	x P	IV:17	1953		F	P	
		18	1955		F	P	
III:15	P x N	IV:19	1950		M	N	
III:17	x N	IV:20	1954		F	N	
IV:2	x N	V:1	1960		F	N	

Pedigree 7.

1	2	3	4	5	6	7	8
		I:1	1853	1899	M		
		2	1847	1931	F		
I:1,2		II:1	1878		M	P	
		2	1882		M	P	
		3	1883	1960	M		
		4	1890		M	P	Proband. Observation, without need for further medical care (793).
		5	1893	1959	M	P	
II:1	P x	III:1	1912		F	N	
II:2	P x	III:2			F		
		3	1908		F	N	
		4			F		
II:3	x N	III:5	1917		M	P	
		6	1923		M	P	
		7	1931		F	N	
II:4	P x N	III:8	1915		F	P	Proband. Nephritis tubularis (590). Cholelithiasis (584).

1	2	3	4	5	6	7	8
		9	1916		M	P	
		10	1926		M	P	
II:5	P x N	III:11	1918		F		
		12	1920	1958	F	P	Proband. Scleroderma (710.0).
		13	1923		M		
		14	1928		F	N	
III:2		IV:1			F		
III:6	P x N	IV:2	1945		M	N	
		3	1947		F	P	Proband. Acute pharyngitis (470).
		4	1950		F	N	
III:7	x N	IV:5	1952		M	N	
		6	1956		F	N	
		7	1957		F	N	
III:9	P x N	IV:8	1946		F	P	
		9	1948		F	N	
III:10	P x N	IV:10	1948		F	P	Proband. Healthy schoolchild.
		11	1950		M	N	
		12	1958		F	P	
III:11a		IV:13	1936		M		
		14	1939		M	P	Proband. Tuberculous adenitis of neck (015).
III:11b		IV:15	1945		F		
		16	1947		F		
		17			M		
		18			M		
		19			F		
III:12	N x P	IV:20	1940		M	N	
III:14	x N	IV:21			F		
IV:1		V:1			F		

Pedigree 8.

1	2	3	4	5	6	7	8
		I:1	1821	1905	M		
		2	1816	1902	F		

1	2	3	4	5	6	7	8
I:1,2		II:1	1843	D	M		
		2	1854	1924	F		
		3	1857	1931	M		
II:2		III:1	1878		F		
		2	1881	1948	M		
		3	1883	1961	M	P	Proband. Hyperplasia of prostate (610), Cardiac infaction (420.1).
		4	1884		M	N	
		5	1886		M		
		6	1888		M	P	
		7	1890		M		Emigr. to N.Amer.
		8	1892		F		
		9	1894	1946	F		
II:3		III:10	1891		F	P	
		11	1895	1957	M	N	
		12	1908		M		
III:3	P x	IV:1	1910		F	P	
		2	1916		F	P	
III:4	N x	IV:3	1928		M		
		4	1929		M		
		5	1930		F		
		6	1932		F		
		7	1937		M		
		8	1941		F		
		9	1946		M		
III:6	P x	IV:10	1918		M		
		11	1921		F		
III:9		IV:12	1921		M	N	
		13	1923		F	N	
		14	1928		F	N	
III:10	N x P	IV:15	1916		F	P	Proband. Observation, without need for further medical care (793).
		16	1920		M	N	
		17	1923		F	P	
		18	1926		M	N	

1	2	3	4	5	6	7	8
III:11	N x	IV:19	1919		M	N	
		20	1921		F	N	
		21	1923		M	N	
		22	1931		M	N	
IV:1	N x P	V:1	1934		F	N	
		2	1944		F	P	
IV:2	N x P	V:3	1944		M	N	
IV:12	N x	V:4	1951		M		
		5	1959		M		
IV:13	x N	V:6	1951		F		
IV:14	x N	V:7	1950		M		
		8	1950		F		
IV:15	N x P	V:9	1940		M	P	
		10	1943		M	P	
		11	1945		M	P	
		12	1950		M	P	
		13	1951		M	N	
		14	1957		M	N	
IV:16	N x N	V:15	1948		M	N	
		16	1948		M	N	
		17	1958		M	N	
IV:17	N x P	V:18	1949		M	P	
		19	1952		M	N	
IV:20	x N	V:20	1951		M	N	
IV:21	N x	V:21	1955		M		
		22	1959		M		
V:1	x N	VI:1	1959		F	N	

Pedigree 9.

1	2	3	4	5	6	7	8
		I:1		D	M		
		2		D	F		
I:1,2		II:1	1864	D	M		
		2		1905	M		
II:1		III:1	1877	1940	F		
		2	1879	1934	M		

1	2	3	4	5	6	7	8
		3	1881	1959	M		
		4	1883		F	N	
		5	1885	1958	F	P	Proband. Cerebral embolism and thrombosis (332).
		6	1887		M	N	
		7	1890		F	P	Proband. Thyrotoxicosis (252.0). Cardiosclerosis (422.1).
		8	1893	1948	F		
		9	1897		F		
		10	1900		F	P	
II:2		III:11	1886	1958	F	P	Proband. Carcinoma ventriculi (151).
		12	1888		M		
		13	1891		M	N	
		14	1893		M		
		15			M		
		16	1894		M		
		17			M		
		18			F		
		19			M		
		20			F		
		21	1912		M	P	Proband. Arteriosclerotic heart disease (420).
		22			M		
		23			F		
III:5	x P	IV:1	1909		M	P	
		2	1913	1949	F		
		3	1917		F	P	
III:6	N x N	IV:4	1923		M	N	
		5	1924		F	N	
III:7	x P	IV:6	1913	1956	M		
		7	1915		F		
		8	1917		M		
		9	1925		M		

1	2	3	4	5	6	7	8
III:8		IV:10			F		
		11			M		
III:9		IV:12	1928		M	P	Proband. Cirrhosis of liver (581).
III:10	N x P	IV:13	1928		F	N	
		14	1929		M	N	
		15	1931		F		
		16	1935		M	N	
IV:1	P x N	V:1	1935		F	P	Proband. Obesity (287).
		2	1937		M	P	
IV:3	N x P	V:3	1946		M	P	
IV:5	x N	V:4	1952		M	N	
IV:6		V:5	1943		F		
		6	1947		M		
		7	1954		M		
IV:8		V:8	1953		F		
		9	1955		F		
		10	1957		F		
IV:9		V:11	1959		M		
IV:13	x N	V:12	1950		M	N	
		13	1954		F	N	

Pedigree 10.

1	2	3	4	5	6	7	8
		I:1		1912	M		
		2		D	F		
I:1,2		II:1	1884	1958	F		
		2	1884		F		
		3	1888	1959	F	P	Proband. Cardiosclerosis (422.1). Congestive heart failure (434.1).
		4	1889		M	P	
		5	1892		M	P	
		6	1894		M	N	

1	2	3	4	5	6	7	8
II:4	P x N	III:1	1930		F	N	
		2	1934		M		
		3	1937		M	P	
		4	1938		F		
II:5	P x N	III:5	1922		M	P	
		6	1923		M	N	
		7	1925		M	P	
		8	1933		F	P	
		9	1938		M	N	
II:6	N x	III:10			F		
III:1	x N	IV:1	1949		F	N	
		2	1951		M	N	
III:5	P x N	IV:3	1945		F	P	
		4	1948		M	P	Proband. Deflected nasal septum (514).
		5	1953		F	N	
III:6	N x N	IV:6	1953		M		
		7	1954		M		
		8	1955		F		
		9	1958		F		
III:7	P x N	IV:10	1954		F	N	
III:8	x P	IV:11			M		
		12			F		

Pedigree 11.

1	2	3	4	5	6	7	8
		I:1	1868	1955	M		
		2	1870	1937	F		
I:1,2		II:1	1891		M		
		2	1893		M	P	Proband. Exudative pleurisy (003.1).
		3	1895	1918	M		

1	2	3	4	5	6	7	8
		4	1897		F	P	Proband. Diabetes mellitus (260). Pernicious anemia (290). Progressive muscular dystrophy (744.1).
		5	1899		M	N	
		6	1901		F		
		7		D	M		
		8		D	F		
		9	1907	1912	M		
II:1	x N	III:1	1926		F	P	
II:2	P x N	III:2	1925		F		
		3	1929		M		
		4	1930		M	P	
		5	1931		M	N	
II:4a	x P	III:6	1918		M	N	
		7	1920		M		
		8	1922		F		
		9	1924		F	P	
		10	1926		F		
		11	1927		F		
		12	1929	1929	F		
		13	1930		M	P	
II:4b	x P	III:14	1936		M	P	
		15	1939		M		
II:5	N x	III:16			M		
		17			M	N	
		18			M	N	
		19			M	N	
III:1	x P	IV:1	1955		M		
		2	1958		M	P	Proband. Menigitis, *H. influenzae* (340.0).
III:2		IV:3			M		
		4			F		
III:4	P x N	IV:5	1955		M	N	
		6	1959		F	P	
III:5	N x N	IV:7	1958		M	N	

1	2	3	4	5	6	7	8
III:6	N x	IV:8	1952		M	N	
III:7a		IV:9			F		
		10			M		
III:7b		IV:11			F		
		12			F		
		13			M		
III:8		IV:14			F		
		15			M		
		16			F		
III:9	x P	IV:17	1949		F		
		18	1957		F		
III:10		IV:19			M		
III:11		IV:20			M		
		21			M		
III:15		IV:22			F		
III:16		IV:23			M		
		24			F		
III:17	N x	IV:25			M		

Pedigree 12.

1	2	3	4	5	6	7	8
		I:1	1853	1880	F		
		2	1851	1934	M		
		3	1851	1943	F		
I:1,2		II:1	1876	1910	F		
		2	1879	1958	M	P	Proband. Hyperplasia of prostate (610).
I:2,3		II:3	1888	1918	M		
II:1		III:1	1904		F		
		2	1905		M	P	Proband. Non-toxic nodular goitre (251).
		3	1908		M	P	
		4	1909		M		

1	2	3	4	5	6	7	8
II:2	P x	III:5	1910		M	N	
		6	1912		M	P	
		7	1915		M	P	
II:3		III:8	1905		F	N	
		9	1909		F	N	
III:1		IV:1	1927		M		
		2	1929		M		
		3	1932		M		
III:3	P x N	IV:4	1954		F	N	
		5	1956		M	N	
III:4		IV:6			F		
		7			F		
III:5	N x N	IV:8	1940		M	N	
		9	1945		F	N	
		10	1949		F	N	
III:6	P x N	IV:11	1943		M	P	
		12	1948		M	N	
III:7	P x N	IV:13	1952		M	P	
		14	1955		M	N	
III:8	N x N	IV:15	1928		M	N	
III:9	x N	IV:16	1941		M		
IV:15		V:1	1952		M		
		2	1955		F		

Pedigree 13.

1	2	3	4	5	6	7	8
1	2	3	4	5	6	7	8
		I:1	1852	1942	M		
		I:2		1896	F		
I:1,2		II:1		D	M		Emigr. to N.Amer.
		2	1890		M	P	
		3		1961	F		
		4		1918	M		
II:2	P x N	III:1	1914		F	P	
		2	1916		M	N	
		3	1922		M	P	
		4	1924		F	P	

1	2	3	4	5	6	7	8
II:3		III:5	1913		M		
		6	1916		F		
		7	1922		M		
		8	1924		F		
II:4		III:9			F		
		10	1918		F		
III:1	N x P	IV:1	1942		F	P	
		2	1952		M	P	
III:2	N x	IV:3	1945		M		
		4	1947		F		
		5	1953		M		
III:4	N x P	IV:6	1947		F	N	
		7	1949		M	N	
		8	1952		M	N	
		9	1955		M	P	Proband. Observation, without need for further medical care (793).
		10	1959		F	N	

Pedigree 14.

1	2	3	4	5	6	7	8
		I:1	1870	1946	M		
		2	1872	1929	F		
I:1,2		II:1	1899		F		
		2	1901		M		
		3	1903		F	N	
		4	1904	D	M		
		5	1905		F	P	
		6	1907		M	N	
		7	1909		F	N	
		8	1912	1944	M		
		9	1912	D	M		
		10	1917		F	P	

1	2	3	4	5	6	7	8
II:2		III:1	1931		M		
		2	1933		M		
		3	1935		F	N	
		4	1939		M		
II:3	x N	III:5	1929		F		
		6	1931		F	N	
II:5	N x P	III:7	1936		M	N	
		8	1943		F	P	
II:6	N x	III:9	1930		F		
		10	1935		M	N	
		11			M		
		12			M		
II:7	x N	III:13	1933		F	N	
		14	1935		M		
		15	1943		M		
II:8		III:16	1939		M		
		17	1941		M		
		18	1943		F		
II:10	N x P	III:19	1943		M	N	
		20	1946		M	P	
		21	1949		F	P	
		22	1952		M	P	Proband. Bronchitis (501).
		23	1959		F	N	
III:2		IV:1	1959		F		
III:6	x N	IV:2	1952		F	N	
III:9		IV:3	1955		M		
III:10	N x	IV:4			F		
		5			M		
III:13	x N	IV:6	1958		F		

Pedigree 15.

1	2	3	4	5	6	7	8
		I:1	1879	1930	M		
		2	1881	1918	F		
I:1,2		II:1	1905		F	N	

1	2	3	4	5	6	7	8
		2	1906		F	P	
		3	1909	1957	M		
		4	1910		M	N	
		5	1913		M	N	
II:2	N x P	III:1	1928		M	P	Proband. Tonsillitis chron. (510.1).
		2	1930		M		
		3	1941		M	N	
II:4	N x N	III:4	1934		M		
		5	1940		F		
II:5	N x N	III:6	1944		M	N	
		7	1959		F		
III:1	P x N	IV:1	1949		F	P	
		2	1951		F	P	
		3	1952		F	P	
		4	1954		F	N	
		5	1956		M	P	
		6	1958		M	P	
III:2	x N	IV:1	1953		M	N	

Pedigree 16.

1	2	3	4	5	6	7	8
		I:1	1875	1952	M		
		2	1881		F	N	
I:1,2	x N	II:1	1900		M		Emigrated to the USA.
		2	1901		F	N	
		3	1903		M		Emigrated to the USA.
		4	1905		F	N	
		5	1907		F	P	Proband. Observation, without need for further medical care (793).

1	2	3	4	5	6	7	8
		6	1909		M		Emigrated to the USA.
		7	1910		M	P	
		8	1912		F	P	
		9	1913		F	P	
		10	1914		M	P	
		11	1917		M		
		12	1918		M		
		13	1919		F		
		14	1922		F		
II:2	N x N	III:1	1922		F	N	
II:5	N x P	III:2	1927		M		
II:7	P x N	III:3	1940		F	P	
		4	1943		M	N	
II:9	N x P	III:5	1942		F	N	
II:10	P x N	III:6	1944		M	N	
		7	1959		F		
II:11		III:8	1945		F		
		9	1958		M		
II:12		III:10	1945		F		
		11	1952		M		
III:1	N x N	IV:1	1944		F	N	
III:2		2	1957		M		

Pedigree 17.

1	2	3	4	5	6	7	8
		I:1		D	M		
		2		1898	F		
I:1.2		II:1		D	M		
		2	1871	1932	F		
		3			F		
		4	1875		F		
		5	1875		F		
		6		D	F		
		7		D	M		

1	2	3	4	5	6	7	8
		8	1884	D	M		
		9	1886		M		
		10	1886	1887	M		
		11			M		
II:1		III:1		D	F		
		2			F		
		3	1907		M	P	Proband. Commotio cerebri (N 852). Fracture of nasal bone (N 802).
		4			M		
		5			M		
		6			M		
		7			F		
II:2		III:8	1895		F	N	
		9	1897		F		
		10	1900		M		
		11	1901		M		
		12	1903		M		
		13	1905		M		
		14	1908		F	P	Proband. Thrombophlebitis (463). Essential benign hypertension (444).
		15	1911		F		
III:8	x N	IV:1	1922		F	N	
III:14	N x P	IV:2	1932		F	P	
		3	1934		F	P	Proband. Acute tonsillitis (473).
		4	1938		M	N	
		5	1941		M	P	Proband. Army recruit.
		6	1944		M	N	
		7	1947		F	P	
IV:1	x N	V:1	1947		M	N	
		2		D	M		
IV:3	N x P	V:3	1954		M	N	
		4	1956		F	N	

Pedigree 18.

1	2	3	4	5	6	7	8
		I:1	1880	1926	M		
		2	1880	1924	F		
I:1,2		II:1	1903		M	N	
		2	1907		M	P	
		3	1908		F	N	
		4	1912		M	P	
		5	1918		F		
II:1	N x	III:1	1925		F		
		2	1928		F		
		3	1930		F		
II:2	P x N	III:4	1931		F	N	
		5	1936		M	P	
		6	1941		M	P	Proband. Dermatophytosis (131).
		7	1946		M	P	
II:3		III:8			F		
		9			M		
II:4	P x N	III:10	1940		F	P	
		11	1944		F	P	
		12	1951		F	N	
II:5		III:13	1945		F		
		14			M		
III:1		IV:1	1949		F		
		2	1956		F		
III:2		IV:3	1951		M		
		4	1957		F	N	
III:3		IV:5	1955		F		
		6	1958		F		

Pedigree 19.

1	2	3	4	5	6	7	8
		I:1	1861	1931	M		
		2	1861	1937	F		

1	2	3	4	5	6	7	8
I:1,2		II:1	1891		M	N	
		2	1894	1961	M		Emigrated to the USA
		3	1895	1959	M	P	Proband. Arterio-sclerotic heart disease (420).
		4	1897	1942	M		
		5	1900		F	P	
		6	1902		F	P	Proband. Gastric ulcer (540).
		7	1904		F	P	
II:1	N x	III:1			M		
II:3		III:2	1924		M		
		3		D	M		
II:5	x P	III:4	1932		F	N	
		5	1935		F	P	
II:7	N x P	III:6	1935		M	N	
		7	1937		F	N	
		8	1940		F	N	
III:1		IV:1	1945		M		
		2	1950		M		
III:2		IV:3			M		
		4			F		
III:4	x N	5	1957		F		

Pedigree 20.

1	2	3	4	5	6	7	8
		I:1		D	M		
		2		D	F		
I:1,2		II:1		D	F		
		2		D	M		
		3		D	F		
		4	1886		F	P	Proband. Diabete-mellitus (260). Pyelonephritis (600.0).
		5	1890		F		

1	2	3	4	5	6	7	8
		6			F		
		7	1896		M		
		8			F		
II:4	x P	III:1	1908		F	P	
		2	1909		M	N	
		3	1912		M	P	
		4	1914		F		
		5	1915		M		
		6		D	M		
		7		D	M		
		8	1927		F		
		9	1929		F		
II:5		III:10	1921		M		
		11	1926		F	P	
III:1	x P	IV:1			M		
		2			M		
III:2	N x	IV:3			M		
III:3	P x	IV:4	1944		M	N	
		5	1946		M	P	
III:4		IV:6			M		
		7			F		
III:8		IV:8			F		
		9			F		
		10			F		
III:9		IV:11			M		
		12			M		
III:10		IV:13					
		14					
III:11	N x P	IV:15	1946		M	P	
		16	1949		M	P	Proband. Scarlet fever (050).
		17	1951		F	P	Proband. Scarlet fever (050).

Pedigree 21.

1	2	3	4	5	6	7	8
		I:1	1849	1932	M		
		2	1852	1932	F		

1	2	3	4	5	6	7	8
I:1,2		II:1		1911	F		
		2	1875	D	M		
		3		D	M		
		4		D	F		
		5		D	M		
		6			M		
		7		D	F		
		8	1890		M		
		9		D	F		
		10	1894		M	P	Proband. Arthritis coxae (725). Spondylosis (723.1).
		11	1897		F		
II:3		III:1			F		
		2	1906		M	P	Proband. Arteriosclerotic heart disease (420).
II:10	P x N	III:3	1937		M	P	Proband. Diabetes mellitus (260).
		4	1945		M	P	
III:2	P x N	IV:1	1935		F	P	
		2	1943		M	P	
III:3	P x N	IV:3	1958		F	P	

Pedigree 22.

1	2	3	4	5	6	7	8
		I:1	1865	1952	M		
		2	1857	1938	F		
I:1,2		II:1	1883	1955	M		
		2	1886	1899	M		
		3	1888		F	N	
		4		D	M		
		5	1892	1956	F		
		6	1895		M	P	
		7	1897		M	N	

1	2	3	4	5	6	7	8
		8	1899		M		
		9	1901		F	P	
II:3	x N	III:1	1914		F		
		2	1916		F		
		3	1919	1937	F		
		4	1923		F		
		5	1931		F		
II:5		III:6	1917		M		
		7	1920		M	N	
		8	1923		M	N	
		9	1934		F	N	
II:6	P x N	III:10	1925		F	P	Proband. Infestation by taenia saginata (126).
		11	1926		M		
		12	1931		M	N	
II:9a	x P	III:13	1925		M		
II:9b	x P	III:14	1938		M		
III:10	x P	IV:1	1957		F	N	
III:11		IV:2			F		
		3			F		
		4			F		

Pedigree 23.

1	2	3	4	5	6	7	8
		I:1		D	M		
		2		D	F		
I:1,2		II:1	1909		M		
		2	1914		M		
		3	1916		F	P	Proband. Furuncle of nose (690.0).
		4	1918		M		
		5	1921		M		
II:3	x P	III:1	1933		M	P	
		2	1939		F	N	
		3	1943		F	N	
		4	1948		M	P	
		5	1955		M	P	

Pedigree 24.

1	2	3	4	5	6	7	8
		I:1	1862	1940	M		
		2	1858	1914	F		
I:1,2		II:1	1889		M	N	
		2	1891	1918	F		
		3	1894		M	P	Proband. Polyneuritis (364).
		4	1900	1902	M		
II:2	N x N	III:1	1915		M	N	
		2	1917		M		
		3	1920		M		
		4	1923		F		
		5	1925		F	N	
		6	1930		M	N	
		7	1933		M		
		8	1934		M		
II:3	P x N	III:9	1927	1928	F		
		10	1929		F	P	
		11	1939		F	P	Proband. Pyelonephritis (600.0).
III:1	N x	IV:1	1950		F		
		2			M		
III:4		IV:3	1952		F		
III:5	x N	IV:4	1960		M		
III:10	N x P	IV:5	1955		M	P	Proband. Acute nephritis (590).

Pedigree 25.

1	2	3	4	5	6	7	8
		I:1	1876	1946	M		
		2	1885	1955	F		
I:1,2		II:1	1906		M	P	

1	2	3	4	5	6	7	8
		2	1915		F		
		3	1917	1959	M	N	
		4			M		
		5			M		
II:1	P x N	III:1	1935		M	P	Proband. Deflected nasal septum (514). Chronic sinusitis (513).
		2	1938		M	N	
		3	1947		M	N	
II:3	N x	III:4			M		
II:4		III:5			F		
		6			F		

Pedigree 26.

1	2	3	4	5	6	7	8
		I:1		D	M		
		2	1898		F		
I:1,2		II:1			M		
		2	1921		M	P	Proband. Prostatitis (611). Pathological personality NOS (320.7).
		3			M		
II:2	P x N	III:1	1941		M	N	
		2	1943		M	N	
		3	1945		F	P	Proband. Bronchitis, allergic (241). Allergic eczema (244).
		4	1950		F	P	

Pedigree 27.

1	2	3	4	5	6	7	8
		I:1	1868	D	M		
		2		D	F		
I:1,2		II:1	1897		M	P	
		2		D	M		
II:1	P x N	III:1	1922		F	P	Proband. Acute nasopharyngitis (470).
		2			M		
II:2		III:3			M	N	
III:1	x P	IV:1	1942		M	N	
		2	1946		F	P	
		3	1951		F	N	
III:2		IV:4			F		
III:3	N x	IV:5			F		
		6			F		

Pedigree 28.

1	2	3	4	5	6	7	8
		I:1	1891		M	P	
		2	1897	D	F		
I:1,2		II:1	1922		F	P	
		2	1924		M		
		3	1925		M	N	
		4	1928		F	P	Proband. Chronic tonsillitis (510).
		5	1936		M	P	
II:4	N x P	III:1	1951		M	N	

Pedigree 29.

1	2	3	4	5	6	7	8
		I:1	1852	1931	M		
		2	1860	1936	F		

1	2	3	4	5	6	7	8
I:1,2		II:1	1884	D	F		
		2	1886		M	P	
		3	1888	D	F		
		4	1890		M		
		5	1891		M		
		6	1893	D	M		
		7	1895		F		
		8	1897		M		
		9	1901		F		
		10	1903	D	F	P	Proband. Arteriosclerotic heart disease (420). Bronchopneumonia (491).
		11	1905		M	N	
II:2	P x N	III:1	1914		M		
		2	1916		M	N	
		3	1918	1961	F		
		4	1941				

Pedigree 30.

1	2	3	4	5	6	7	8
		I:1	1862	1936	M		
		2	1861	1941	F		
I:1,2		II:1	1885		F		
		2	1887		F		
		3	1893		F		
		4	1895		F		
		5	1900		F		
		6	1904		F	P	Proband. Cholecystopathia (585). Transposition of viscera (759.3).
II:6	N x P	III:1	1943		M	P	

Pedigree 31.

1	2	3	4	5	6	7	8
		I:1	1872	1959	M		
		2	1867	1946	F		
I:1,2		II:1	1905		F	P	
		2	1906		M		
		3	1907		M	N	
II:1	x P	III:1	1934		M	P	Proband. Blood donor.
		2	1942		M	N	
II:3	N x	III:3			M	N	
		4			M		

Pedigree 32.

1	2	3	4	5	6	7	8
		I:1	1853	1931	M		
		2	1849	1924	F		
I:1,2		II:1	1885		F	N	
		2	1886		F	P	
		3	1888	1960	M	P	Proband. Duodenal ulcer (541).
		4	1890		M	P	
		5	1891		M		

Pedigree 33.

1	2	3	4	5	6	7	8
		I:1	1850	1935	M		
		2	1858	1935	F		
I:1,2		II:1	1880		F		
		2	1885	D	M		
		3	1887		M		
		4	1888		F	P	

1	2	3	4	5	6	7	8
		5	1891		F	P	
		6	1893		M	P	Proband. Herpes zoster, opthalimic (088).
		7	1896		M	P	Proband. Duodenal ulcer with melaena (541.0).
		8					Emigrated to the USA.
		9					Emigrated to the USA.
		10					Emigrated to the USA.
		11		D			
		12		D			
		13		D			
		14		D			
		15		D			

Pedigree 34.

1	2	3	4	5	6	7	8
		I:1	1890	1946	M		
		2	1891	1924	F		
I:1,2		II:1	1914		M	P	Proband. Albuminuria NOS (789.0).
		2	1916		M		
		3	1918		M		
II:1	P x N	III:1	1944		M	N	
		2	1946		M	N	
		3	1952		F	N	

Pedigree 35.

1	2	3	4	5	6	7	8
		I:1	1882	1947	M		
		2	1881	1947	F		
I:1,2		II:1	1907		F	P	Proband. Displacement of intervertebral disc (735).
		2	1908		F	P	
		3	1910		M		
		4	1915	1936	M		
		5	1918		F		
II:1a	x P	III:1	1936		M	N	
II:1b	x P	III:2	1950		M		
		3	1951		M		
II:2	x P	III:4	1932		M		
		5	1939		M		
		6	1949		F		

Pedigree 36.

1	2	3	4	5	6	7	8
		I:1		D	M		
		2		D	F		
I:1,2		II:1	1908		M		
		2	1912		M	P	Proband. Pyralysis of abducense nerve (367).
		3	1916		F		
		4	1919		F		
II:2	P x N	III:1	1942		M	P	

Pedigree 37.

1	2	3	4	5	6	7	8
		I:1		D	M		
		2		D	F		

1	2	3	4	5	6	7	8
I:1,2		II:1	1886		F	P	
II:1	N x P	III:1	1915	1948	M		
III:1	x N	IV:1	1934		F	P	Proband. Headache NOS (791).
IV:1	N x P	V:1	1951		M	P	

Pedigree 38.

1	2	3	4	5	6	7	8
		I:1			M		
		2			F		
I:1,2		II:1	1880	1958	F	P	Proband. Essential benign hypertensive heart disease (440). Cholecystopathia (585).
II:1	x P	III:1	1916		M		
		III:2	1918		M		
		III:3	1920		M		
		III:4	1924		F		
III:1	x N	IV:1	1941		M	P	
III:4		IV:2	1948		F		

Pedigree 39.

1	2	3	4	5	6	7	8
		I:1	1876	1949	M		
		2	1884		F	N	
I:1,2	x N	II:1			M		
		2			M		
		3			M		
		4	1913		M	P	Proband. Blood donor.
		5	1916		M	N	
		6			M		

1	2	3	4	5	6	7	8
		7			F		
		8			F		
		9			F		
II:5	N x N	III:1	1946		M	N	
		2	1949		F	N	
		3	1956		M	N	

Pedigree 40.

1	2	3	4	5	6	7	8
		I:1		D	M		
		2		D	F		
I:1,2		II:1	1909		M	P	Proband. Spondylitis deformans (723.1).
		2	1915		M	N	
II:1	P x	III:1	1943		M		
		2	1946		F		
II:2	N x	III:3			M		
		4			M		
		5			M		

Pedigree 41.

1	2	3	4	5	6	7	8
		I:1	1875	1935	M		
		2		D	F		
I:1,2		II:1	1915		M	P	
		2	1917		M	P	Proband. Lichen planus (707).
		3	1923		F	N	
II:3	x N	III:1	1945		F	N	
		2	1948		M	N	

2. Primary data on probands whose families were not examined.

No.	Year of Birth Death	Sex	Pheno-type	Comments.
1[1])	1905	F	P	Diabetes mellitus (260).
2	1927	F	P	Hypothyroidism (253).
3	1882	F	P	Cardiosclerosis (422.1). Pulmonary tuberculosis (002).
4	1897	F	P	Otosclerosis (396).
5	1940	M	P	Chronic sinusitis (513).
6	1917	M	P	Spondylarthrosis (723.1). Oligophrenia (325.5).
7	1922	M	P	Anxiety neurosis (310).
8[2])	1899	F	P	Influenza with pneumonia (480). Stenosis of mitral valve (410).
9	1904	M	P	Pulmonary emphysema (527.1). Essential benign hypertension (444).
10	1899	F	P	Bronchiectasis (526).
11[3])	1947	F	P	Healthy schoolchild.
12	1940	M	P	Army recruit.
13	1941	M	P	Army recruit.
14[4])	1941	M	P	Army recruit.

[1]) No. 1 and No. 9 are sibs. [2]) No. 8 is a far relative of No. 12. [3]) No. 11 is a far relative of pedigree 39. [4]) No. 14 is a far relative of pedigree 14.

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